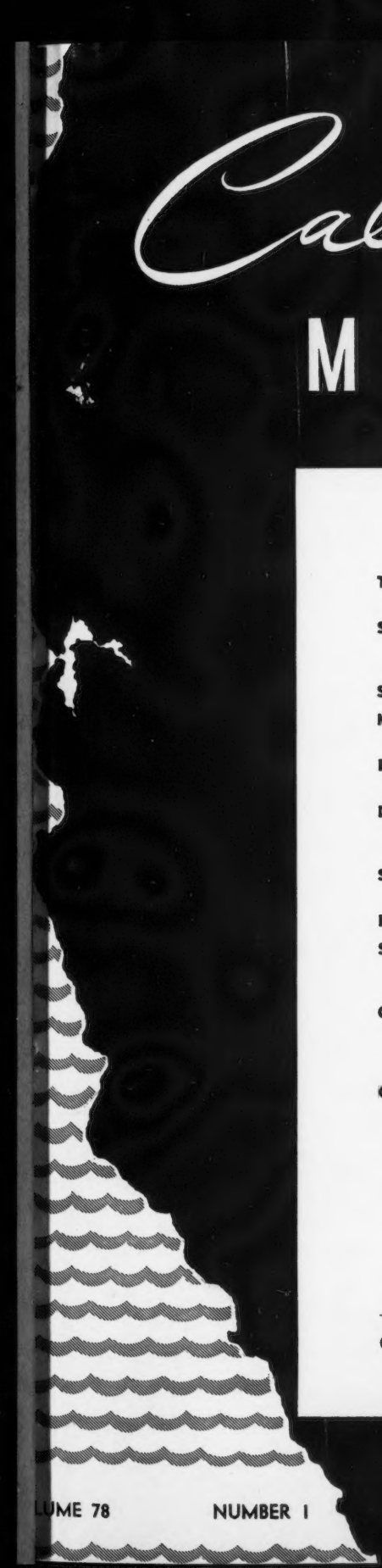

California MEDICINE

JANUARY 1953

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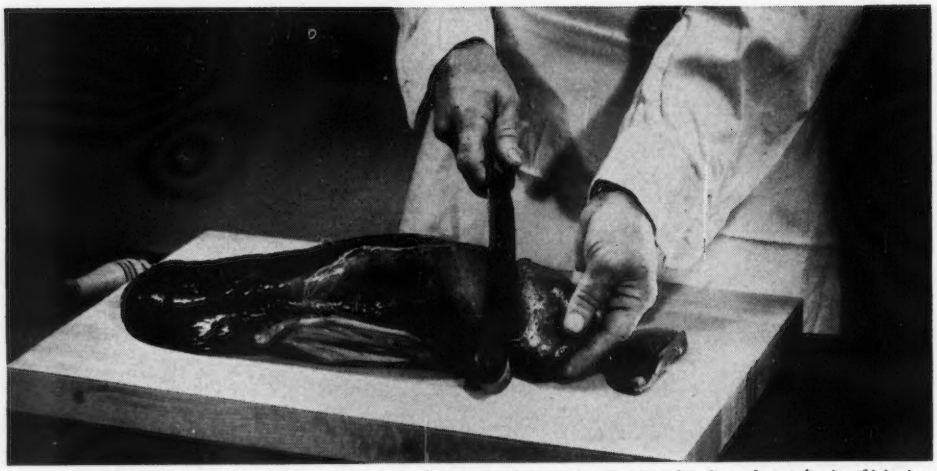

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The Two Kinds of Death of William Harvey

WILLIAM S. McCANN, M.D., Rochester, N. Y.

• The determining factors in congestive heart failure as well as in shock are more often extracardiac than in the heart itself. Carbon dioxide tension in the blood is as important as the oxygen tension. Carbon dioxide is a hemodynamic agent of the first magnitude. It can be quickly increased or decreased by altering the ventilation of the lungs. It is a prime factor in determining whether the circulation fails from a lack or from suffocation by an excess.

IN THE FAMOUS DE MOTU CORDIS in 1628 William Harvey made the following statement:

"This is evidence of two kinds of death, failure from a lack, and suffocation from an excess. In these examples of both, one may find proof before his eyes of the truth spoken about the heart."

After more than three centuries we can translate this statement of Harvey into modern terms. If we apply them to the circulation, we have for "failure from a lack" all the conditions characterized by "*shock*"; while for "suffocation from an excess" we have the various forms of "congestive failure" of the circulation. The *lack* in shock is basically the lack of the volume of blood in circulation: The venous system is underfilled, the venous return is lessened, the output of the heart is thereby diminished and its contractions become rapid and weak. The "excess" in congestive failure may be applied to an excess of volume of blood in circulation: The veins are overfilled, the volume of blood in the lungs is increased, the output of the left ventricle may be high or low, depending upon circumstances which we will discuss later; but, high or low, the output of the left ventricle is less than it was before the onset of decompensation or failure and in any case is inadequate to meet metabolic demands.

Both types of failure of the circulation may occur while the heart is normal but, whether the heart is normal or abnormal, events taking place outside the heart determine whether the circulation fails from *lack* or from *excess* of effective blood volume.

We see, for instance, that when a coronary artery is occluded the patient may first exhibit evidence of *shock*. The same thing is generally true when myocarditis, such as that of diphtheria, develops. *Congestive failure*, if it follows myocardial injury, is usually a secondary event and owing to factors outside the heart, but principally operating in the lungs which, as I shall try to show you, are the site at which the type of circulatory failure is determined. You will recall that in Carl Wiggers' laboratory Levy and Berne[7] tried in many ways to produce congestive failure in experimental animals. They produced many types of injury to the heart without causing congestive failure. The only method which succeeded was that of putting a constricting band around the pulmonary artery. By this means they were able to reduce the output of the left ventricle significantly, without incurring a drastic fall in arterial pressure, and at the same time to raise the pressure in the right ventricle and the right auricle.

The right and left sides of the heart are, in a

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Guest Speaker's Address presented before the Section on General Medicine at the 81st Annual Session of the California Medical Association, Los Angeles, April 27-30, 1952.

sense, two separate organs, with the pulmonary, the bronchial, and the coronary circulations connecting them.

Traditional thinking about the heart has been to regard the pulmonary circulation as being a very *passive* mechanism for transfer of blood from the right ventricle to the left auricle. Today we have learned that it is *not passive*, but one which by its activity creates a variable resistance to this transfer of blood from right to left. Increase in this pulmonary resistance may accomplish the same result that Levy and Berne produced by a band applied to the pulmonary artery.

The Scandinavian workers v. Euler and Liljestrand[3] showed that the induction of anoxia raised the pulmonic pressure in cats; while the Dutch investigators Dirken and Heemstra[1] showed that this was brought about by the formation of histamine in the lung. Histamine, when acting directly on the pulmonary vessels, causes constriction of the vein and artery and dilatation of the pulmonary capillaries, according to Durwood Smith.[12] It has also been shown that in man the induction of anoxia will raise the pulmonic pressure, as measured by catheterization of the heart; and in experimental work observed by the author it was found that this effect is augmented by increasing the tension of carbon dioxide in the blood. Highly significant correlations have been observed between the tension of carbon dioxide of the mixed venous blood and the ratio of residual air to total pulmonary capacity.

The lack of oxygen and accumulation of carbon dioxide then may increase the vascular resistance to the transfer of blood from the right ventricle to the left auricle. In certain circumstances this resistance can be raised to a level at which the output of the left ventricle is decreased and the pressure raised in the pulmonary artery, the right side of the heart, and the veins. This variable resistance to flow of blood through the lungs is owing only in part to the smooth muscle in the walls of pulmonary arteries and veins. The pressure of air within the alveoli may also increase the resistance to flow through the alveolar capillaries. The importance of this latter factor was strikingly demonstrated by discovery of the mechanism of "tussive syncope,"[10] which had previously been termed "laryngeal epilepsy" by Charcot. A person was observed who had paroxysms of cough which led to syncope followed by convulsions. By catheterizing the heart it was observed that the pulmonary arterial pressure rose to more than 200 mm. of mercury during paroxysmal cough, while the cardiac output and arterial pressure fell to very low levels. The same phenomena occur to a lesser degree in a Valsalva experiment. They must also be quite similar to those occurring in anaphylactic shock, in which the alveoli become immensely distended, the left side of the heart nearly empty, and the right side engorged with blood.

Most of the recent discussions of the mechanism of congestive failure of the circulation have had to do with the failure of the circulation to deliver enough blood to the tissues to supply the oxygen required by them. But there is fallacy in attempting to explain the phenomena upon the basis of oxygen lack alone.

If a normal man goes to an altitude in the high Andes, the lack of oxygen increases the ventilation of his lungs to a point at which he pumps out carbon dioxide, and increases the alkalinity of his blood, producing the phenomena of "mountain sickness," which are those of "shock." One may observe similar phenomena in carbon monoxide poisoning, in which similar hyperventilation results in hypocapnia and shock; and this may be the case also in alveolar or lobar pneumonia.

On the other hand, it was learned during the war that when healthy men in heavy bombers were cut off from their oxygen supply at levels of 30,000 to 35,000 feet, they died in about six minutes; and the anatomical conditions observed at autopsy were those of congestive failure. In 1934 Hurtado, Kaltreider and I[5] produced a similar condition in guinea pigs at only 16,000 feet (simulated altitude in a low pressure chamber). We men, who were in the chamber with the guinea pigs, found that our lungs reacted in such a way as to lower the vital capacity and increase the residual air. These changes are such as would aid in preventing or diminishing the loss of carbon dioxide from anoxic hyperventilation, and are among the mechanisms responsible for acclimatization or adaptation to life at high altitude or other forms of chronic anoxia. Such changes—as diminished vital capacity and increased residual air —are regularly observed in congestive failure of the circulation.

The lungs of guinea pigs which we took with us into the low pressure chamber showed congestion of the alveolar capillaries. We did not know it at that time, but such changes are consistent with recent demonstration that histamine is produced in the anoxic lung. Histamine causes capillary dilatation and sluggish flow. It also causes contraction of the pulmonary artery and vein.

To summarize the foregoing: The initial response to anoxia is hyperventilation and hypocapnia and alkalosis and a tendency to shock. With persistence of anoxia lowered vital capacity and increased residual air tend to reduce loss of carbon dioxide. Deeper anoxia, by causing formation of histamine; increases pulmonary vascular resistance and dilatation of alveolar capillaries. At very high altitudes, 30,000 to 35,000 feet, anoxia results in death of

persons with normal hearts in six minutes, and at necropsy the changes observed are those of congestive failure.[8]

The foregoing sequence of events may occur in the development of congestive failure due to abnormality of the heart, so that it cannot increase its output sufficiently to meet metabolic demands. When congestive failure is due to heart damage, the developing anoxia causes hyperventilation and hypocapnia (low alveolar and arterial carbon dioxide tensions), and an initial tendency toward shock may be observed, as in left ventricular infarction. The sequence of events which mark the transition to congestive failure can be beautifully explained by the nature of changes occurring in the lungs. The increased pulmonary resistance, due to both vascular and bronchial changes, raises the pressure in the right heart and veins. This reaction would serve to protect the weakened left heart from "suffocation by an excess" of blood driven into it by a stronger right heart. I have referred to this as the "check valve" action of the lung, but I am not sure it is a good term to describe the protective variable resistance by which the lung prevents overdilation of a weakened left ventricle. A further aspect of this protective action is to be seen in the fact that excess blood thrown into alveolar capillaries may be recirculated back to the right heart through the bronchial veins. These bronchial veins are distended and in long-standing heart disease such as mitral stenosis varicosities develop from which the blood spitting of this disorder may occur.[4]

The reaction of a normal ventricle to increase in vascular resistance to its discharge is to increase its output; and conversely, when the output of a ventricle decreases, the vessels into which it discharges tend to constrict to accommodate a lesser input. Thus as the resistance in the anoxic lung may increase the right ventricular output, the excess blood thrown into it may be drained off through the bronchial veins, and at the same time the lessened output of the left ventricle would be discharged into constricted arterioles. This may be one of the principal reasons why the kidney then produces less urine and retains salt and water.

The development of edema and the building up of the circulating blood volume represent a complex series of events. With the output of salt and water by the kidneys diminished, ingestion of salt and water will produce an increase in body water and weight. In the capillaries of the body, permeability is increased by anoxia—and lymph is formed at an excessive rate. As the lymph sacs fill, the flow of lymph through the thoracic duct would meet the resistance of rising venous pressure. Ultimately the rising volume of lymph and tissue water will raise tissue pressure to the point at which lymph will flow from duct to vein, and also will drive venous blood to the right auricle with increasing pressure. A balance between rising lymph and venous pressure may ultimately be struck at a higher level of blood volume.

The failure of the lung to maintain adequate ventilation results in a form of congestive failure of the circulation which differs in several important respects from that which we have described following a primary injury to the heart: The high resistance of the lung to transfer of blood is a primary condition of the failure, instead of being built up gradually as a secondary phenomenon; there is anoxia with hypercapnia in contrast to the anoxia with hypocapnia of initial heart failure. In primary pulmonary failure the blood volume is as high as it becomes in heart failure, but in the former the circulation time is greatly shortened and even when congestive failure occurs the circulation time may be found within normal limits, and the resting cardiac output may remain within normal limits. Secondary hypercapnia may occur due to changes within the lungs, which tend to compensate the initial hypocapnia.

This contrasting set of conditions led McMichael[11] to divide congestive failure into two types—one with high and one with low cardiac output. The high output failures are those in which the heart is relatively normal and in which the right ventricle is threatened with "suffocation with an excess" of venous blood rushing down upon it like a flash flood in an arroyo. The situation of the right ventricle is somewhat like that of the left ventricle in the case of primary heart failure, in that the damaged left heart might be overwhelmed by the normal output of the right heart were it not protected by increased resistance in the lung.

Are there any "check valves" which can protect the right heart in the same way in which the lungs protect the left? It would seem likely that the liver is capable of functioning in this capacity. Dock and Tainter[2] introduced the idea of an hepatic sphincter, and this became a much disputed point. It seems likely, in the light of more recent work, that there may be multiple small sphincters in the liver at the point where the liver sinusoids enter the central lobular vein. These sphincters are relaxed in thiamine deficiency and this may be one of the reasons why in persons with beri beri the heart shows a high output in failure.

The carbon dioxide tension may also regulate the patency of these sphincters. High tensions of carbon dioxide in general produce dilatating effects on the vascular system, but there is some evidence that the portal blood flow is retarded (possibly at the central lobular end of the sinusoids). It offers an attractive hypothesis that hypercapnia constricts

the hepatic sphincters, but the evidence is not entirely clear. As "check valves" the liver and the lungs have many analogies. The normal main inflow is venous in each, the arterial supply, hepatic or bronchial, has a nutrient function and offers collateral channels with numerous anastomoses — which may act as shunts.

Arteriovenous anastomoses and shunts play a large role in the "high output" failures. Their patency is increased in the hypercapnia of the failing lung, and in the thiamine deficiency of beri-beri. Arteriovenous aneurysms lead ultimately to high output failures. The enlarged vascular channels in the bones in Paget's osteitis deformans have a similar effect. All of these conditions require a larger circulating blood volume and afford rapid transfer of blood from the arterial to the venous side, and create a continued threat of overwhelming the right heart by a flood of venous blood. Factors which would increase the vascular resistance in the liver and in the lung (the check valves) would have a protective function on the respective ventricles, preventing them from being overwhelmed by an onrushing flood. Probably we should no longer speak of "passive congestion" of the lungs or of the liver. Congestion appears to be due to activity and not passivity within the circulation of these organs, brought about by the action of substances like histamine, and by changing tensions of carbon dioxide and oxygen and of electrolytes.

The "low output type" of congestive failure is the one most generally associated with abnormality of the heart, while the "high output type" is the result of abnormality of extracardiac mechanisms. Low output failure is the more likely to respond to digitalis, which is notoriously unreliable in high output failure. Low output failure, at least in its earlier stages, can be roughly equated with hypocapnia; and high output failure with hypercapnia. Opiates may be useful in low output failure by decreasing overventilation and decreasing loss of carbon dioxide. On the other hand morphine tends to increase hypercapnia of high output failure, and may be lethal in its effect.

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Serum Lipids in Normal and Abnormal Subjects

Observations on Controlled Experiments

LAURANCE W. KINSELL, M.D., GEORGE MICHAELS, Ph.D., LOREN DeWIND, M.D., JOHN PARTRIDGE, M.D., and LENORE BOLING, M.D., *Oakland*

• The relationship of diet to serum lipids and to atherosclerosis is a controversial subject. The data presented indicate that diets containing very large amounts of vegetable fat are consistently associated with a sharp fall in serum cholesterol and phospholipid, whereas administration of equal amounts of fat of animal origin is associated with a rise of the serum lipids to levels noted on an average mixed diet.

In critical evaluation of elderly hospitalized diabetic patients with advanced atherosclerosis it was observed that there was close mathematical correlation between serum content of cholesterol, "lipoproteins," and phospholipids. There was no obvious correlation between the degree or kind of atherosclerosis and any one of the lipid entities followed. Coronary occlusion occurred in a patient with one of the lowest levels of cholesterol and of lipoprotein.

FOR MORE THAN two generations the pathogenesis of atherosclerosis has been a controversial subject. Despite the improvement in chemical techniques, and in the understanding of some aspects of lipid metabolism, recent additions to the literature have tended to confuse further rather than to clarify. Perhaps the greatest single reason for this has been the tendency on the part of some investigators to confuse theories with facts, and prematurely to attach clinical significance to inadequately controlled laboratory observations. It may, therefore, be well to consider briefly which portions of the field are truly in a factual state and which are theoretical.

Many of the papers on which the following statements are based are reviewed in an excellent paper by Weinhouse.[6]

FACTS

The following concepts regarding atherosclerosis appear to be unequivocal:

1. There is an increasing incidence with age.
2. The incidence is high in patients with diabetes.
3. There is increased incidence in obese persons.
4. There is increased incidence in some, but not in all, patients with hypercholesterolemic atheromatosis.[7]

THEORIES

To attempt to cite all the theoretical material would entail voluminous report. Following, however, are some of the more interesting controversial statements:

1. A high intake of dietary fat predisposes to atherosclerosis.
2. A diet high in cholesterol predisposes to atherosclerosis.
3. "Lipotropic agents" prevent or favorably modify atherosclerosis.
4. Atherosclerotic subjects have larger amounts of lipids, particularly cholesterol, in the serum than do others.
5. Patients with atherosclerosis have a greater than normal amount of certain "giant molecules" (lipoprotein Sf_{10-20}) in the serum.[2]

At one time or another each of the foregoing statements has been enthusiastically acclaimed as being factual. To many an unprejudiced observer, none of them, when subjected to objective scrutiny, has been acceptable.

LABORATORY AND CLINICAL OBSERVATIONS

Two groups of data will be presented here. In one group are data on observations of patients whose dietary intake was chemically constant (by formula) and who were studied over long periods on the metabolic ward of Highland Alameda County Hospital. In the other group are data on observations (some of them previously reported elsewhere) of patients in the wards of the chronic disease hospital that is associated with the same hospital.

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Dr. Partridge is a Schering Research Fellow in endocrinology.

These studies have been supported in part by grants from the National Institutes of Health and from the Armour Laboratories.

Presented before the Section on General Medicine at the 81st Annual Session of the California Medical Association, Los Angeles, April 27-30, 1952.

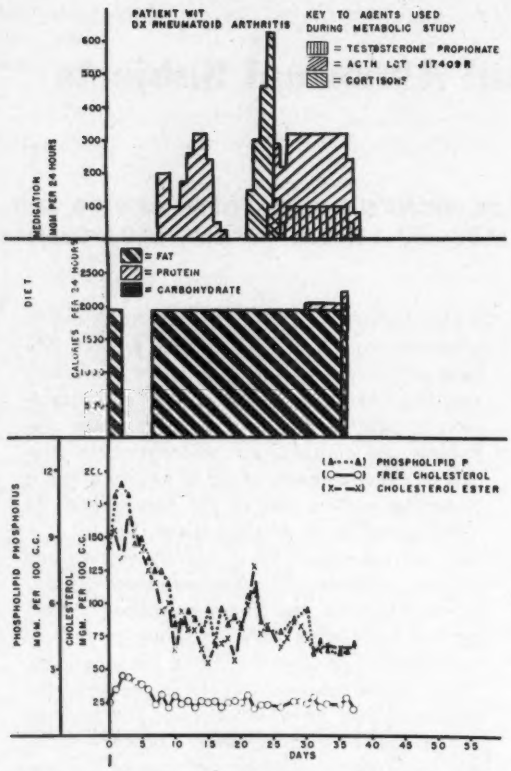

Chart 1.—Changes in serum lipids during "pure fat" intake.

METHODS

Lipid phosphorus was determined by the method of Youngburg and Youngburg.[8] Cholesterol and cholesterol esters were determined by the method of Michaels and co-workers,[4] a modification of the Schoenheimer-Sperry technique.[5] Lipoproteins were quantitated by an ultracentrifugation technique.*

Dietary Modification of the Level of Certain Serum Lipids

These data were obtained in the course of somewhat extensive studies dealing with various aspects of lipid metabolism in human subjects. As part of a program designed to evaluate hormonal factors which regulate fat oxidation, it was necessary to maintain patients on pure fat diets and on diets containing only fat and protein. These diets, in most instances, were administered at hourly intervals throughout the 24 hours through a polyethylene tube, the tip of which lay in the duodenum. The fat, unless otherwise indicated, was of vegetable origin.

In Chart 1 will be noted the changes in serum content of esterified and free cholesterol and of phospholipids in a patient maintained on a pure fat diet over a period of approximately a month. It will be noted that in this patient, a rather precipitous fall in serum cholesterol esters occurred, with an equivalent fall in phospholipids; and that this fall was maintained throughout the period for which the diet was administered. Initially, it was thought that this change in serum lipids was referable to hormonal therapy, but subsequently this was found to be incorrect (see below).

In Chart 2 is recorded another study in a patient with acromegaly and diabetes who also had pronounced decrease in the serum content of the lipids above noted. The fall in total cholesterol approached 150 mg. per 100 cc. of serum.

Chart 3 gives data on a similar study of a patient with thyrotoxicosis. A decrease in serum content of lipids was maintained during the period of high fat diet, but there was a rapid return of the content of lipid entities to previous levels when the patient resumed an average mixed diet. The rise occurred despite the continuation of hormonal therapy.

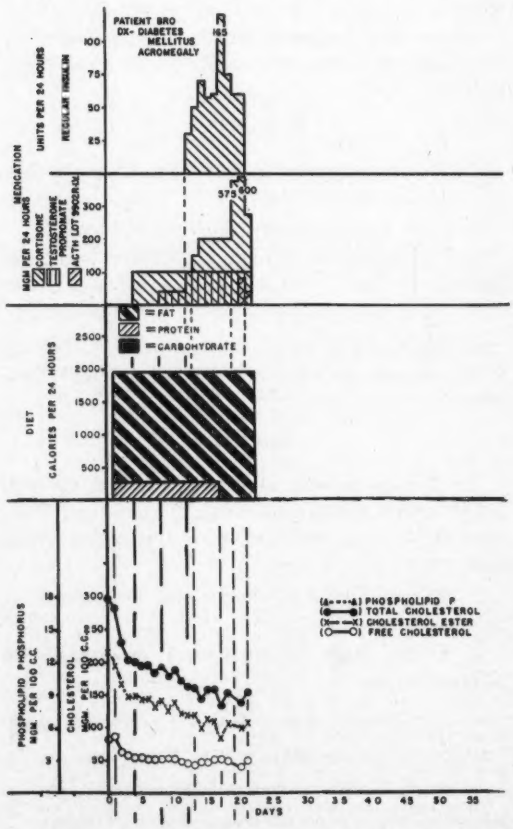

Chart 2.—Serum lipid changes during fat-plus-protein, and then pure fat intake.

*Grateful acknowledgment is made to Dr. John Gofman for performance of these determinations.

The preceding observations obviously raised, among others, the question as to whether these changes in serum lipids were related specifically to some factor present in the vegetable fat, or whether they were referable to the absence of cholesterol or of other sterol or phospholipid entities normally present in a mixed diet. With this in mind a patient in whom a change similar to that noted above had occurred was placed on a diet high in vegetable fat, to which was subsequently added 30 grams and later 60 grams of cholesterol a day (Chart 4). It will be noted in the chart that no maintained increase in serum content of cholesterol or phospholipids occurred during the period of ingestion of the huge amount of cholesterol. Analysis of the stool indicated that the greater portion of the administered cholesterol had been absorbed, although a considerable amount was contained in the stool. Inasmuch as the period of cholesterol administration was short, it is possible that long continued cholesterol administration might have produced some change in cholesterol content in the serum. (This possibility is now being investigated.)

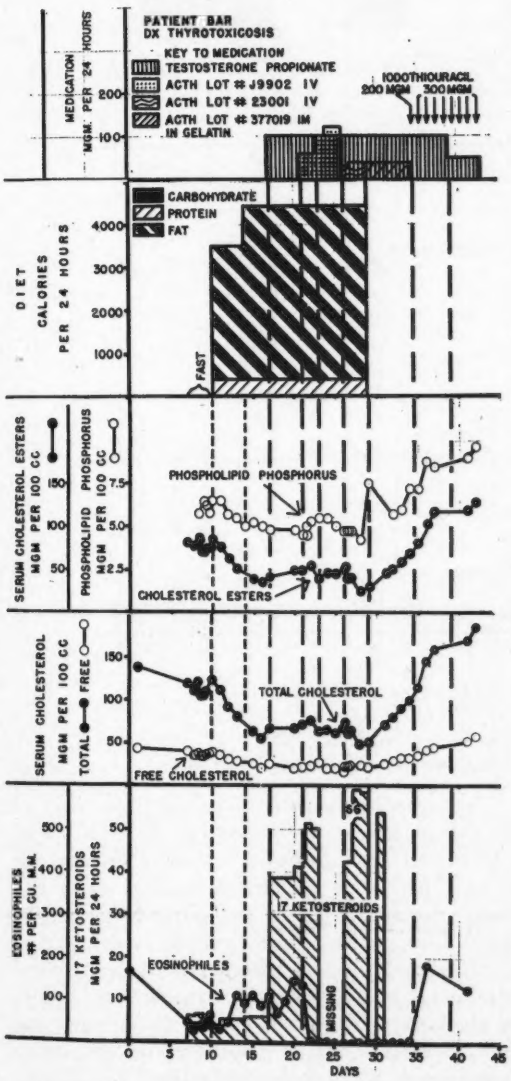

Chart 3.—Increase in serum lipids following substitution of an average mixed diet for a high fat, low protein diet.

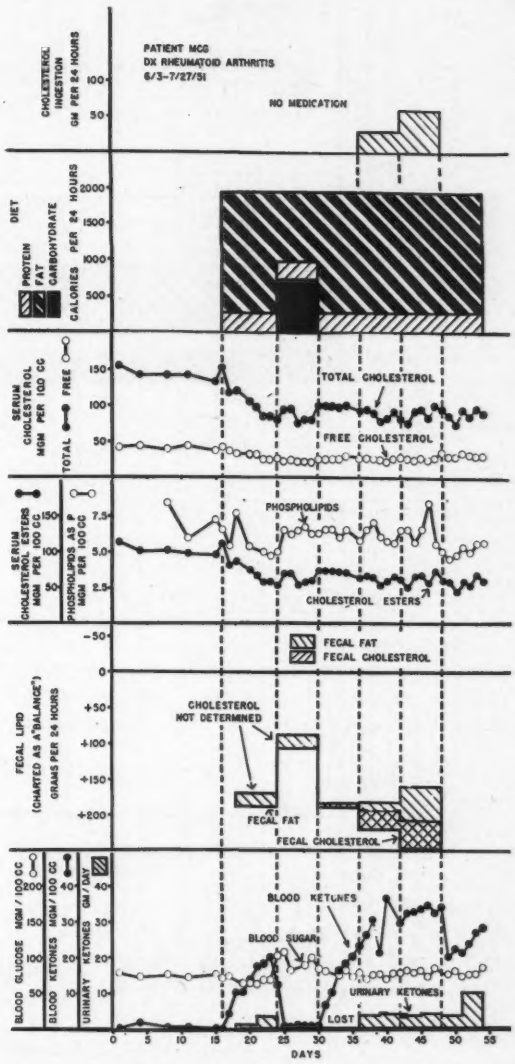

Chart 4.—Effect of addition of cholesterol to vegetable fat, upon serum lipids.

From the foregoing it may be concluded that the ingestion of a large amount of vegetable fat is compatible with a rather striking fall in the serum

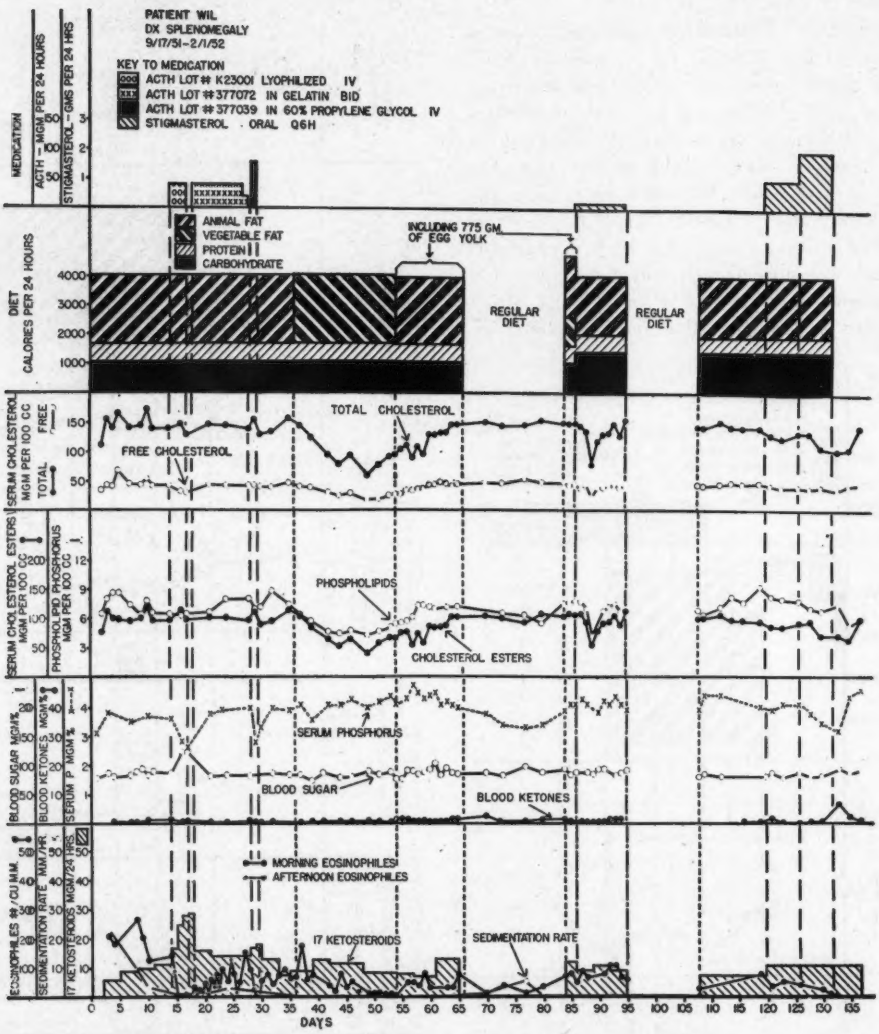

Chart 5.—Effect of different dietary fats upon serum lipids.

content of certain lipids. Similar observations were made in 14 patients, all studied for rather long periods.

Studies also were carried out in which patients received equal amounts of fat, of vegetable, animal and egg yolk origin, respectively, for stated periods. The results are given in Chart 5. From this and other studies, it was apparent that the ingestion of very large amounts of fat of animal and egg yolk sources (the total egg yolk being equivalent to 36 eggs daily) resulted in serum content of cholesterol and phospholipid essentially identical with the content of these factors in persons receiving an average mixed diet. That serum content of lipids decreases when vegetable fat is the source of dietary fat was further confirmed.

Studies on Diabetics with Advanced Atherosclerotic Changes

The following data were obtained from study of 24 elderly patients with diabetes, all with major evidence of atherosclerosis, including extreme degrees of peripheral vascular disease and major evidence of coronary artery and cerebrovascular disease.[1] These patients were receiving relatively constant "diabetic" diets. Specimens of blood were obtained at frequent intervals throughout the period of observation. The serum content of esterified and free cholesterol and of phospholipids was determined and in addition the lipoprotein (Sf_{10-20}) content was determined by tests of samples of the same specimens of blood that were used in determining

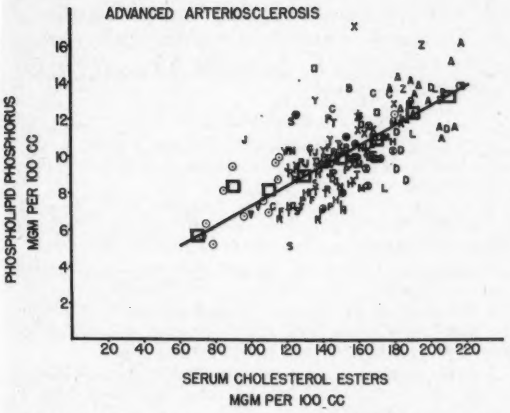

Chart 6.—Correlation of serum phospholipids and cholesterol esters in a group of elderly diabetic atherosclerotic patients. The correlation index is 0.671.

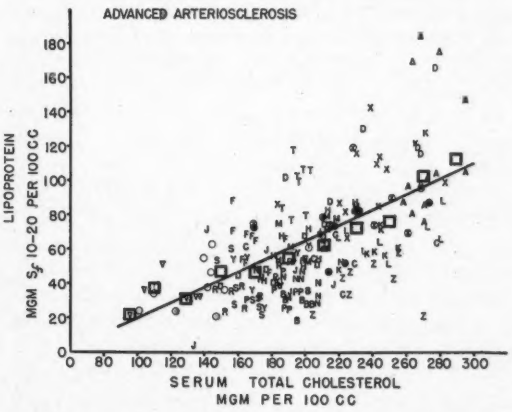

Chart 7.—Correlation between serum "lipoprotein" and total cholesterol. The correlation index is 0.613.

the content of the other lipids. The objectives of the study were two:

1. To determine whether there was any obvious correlation between the atherosclerotic status of the patient and the content of any lipid fraction in the serum.

2. To determine whether there was any obvious correlation between any or all of the lipid entities studied.

In Chart 6 are shown the phospholipid and cholesterol ester data plotted against one another on a linear scale. It will be noted that there was a remarkable scatter of values, and further that there was a pronounced "linear" mathematical correlation between the phospholipid phosphorus and the serum cholesterol esters with a correlation index of 0.671.

In Chart 7 are shown the observations with regard to the aggregate amounts of all the cholesterol and of all the lipoprotein fractions studied. Here also there

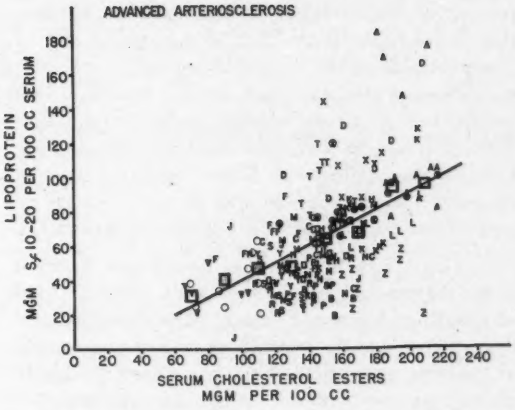

Chart 8.—Correlation between serum "lipoprotein" and cholesterol esters. The correlation index is 0.530.

was pronounced scatter insofar as both entities were concerned, and rather impressive "linear" correlation. The index of correlation was 0.613.

Chart 8 gives a similar comparative evaluation of the data in regard to the lipoprotein and serum cholesterol esters.

From the foregoing data it is apparent that rather close correlation existed between lipoproteins and total cholesterol, lipoproteins and cholesterol esters, and phospholipids and cholesterol esters.

It is apparent also that in this group of patients, all of whom had advanced atherosclerosis, a very wide scatter of all lipid values existed (the range for total cholesterol 134 to 272 mg. per 100 cc.; for lipoprotein, 29 to 176 mg. per 100 cc). In no instance was there obvious correlation between clinical status and the serum content of *any* lipid. The one patient in this series who had a coronary occlusion during the course of the study had the lowest value for cholesterol (134 mg. per 100 cc. of serum) and the third from the lowest value for lipoprotein (33.5 mg. per 100 cc. of serum).

It may be of some interest that the average serum content of cholesterol and phospholipids was significantly higher in this group than in a group of nondiabetic elderly persons without obvious clinical evidence of atherosclerosis, who were hospitalized in the same institution.

CONCLUSIONS

No positive clinical implications are suggested or intended insofar as the preceding data are concerned. It is possible that at a later date some such implications may appear. On the basis of the data, however, the following rather unequivocal statements may be made:

1. The intake of a large amount of vegetable fat is compatible with a quite impressive fall in serum

content of cholesterol and phospholipids. Whether this is referable to the lack of cholesterol and of phospholipids in the vegetable fat, or to the *presence* of some material which actually modifies lipid metabolism, or to the absence of factors in other foods that are in a normal diet, is at present unknown. The addition of a very large amount of cholesterol to the high-fat diet in one instance resulted in no increase in serum content of cholesterol.

2. There was no obvious correlation between serum content of any of the lipids studied (total cholesterol, cholesterol esters, phospholipids, and lipoprotein) and the severity or rate of progression of the atherosclerotic process in a group of elderly diabetic patients with advanced atherosclerosis.

3. Close linear correlation was observed between the serum content of phospholipids and of serum cholesterol esters; between lipoproteins and serum cholesterol esters; and between lipoproteins and serum total cholesterol. The index of correlation between cholesterol and lipoprotein was almost identical with that reported by Keys[3] in reevaluation of data previously reported by Gofman and co-workers.[2]

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Subperitoneal Hemorrhage

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• Clinical diagnosis of subperitoneal hemorrhage can be made in a substantial percentage of cases by recognition of a quite constant syndrome—provided the possibility of bleeding is considered. Progressive anemia, as indicated by repeated counts of erythrocytes in the blood or by hematocrit determinations, is confirmation of the diagnosis.

The majority of patients recover spontaneously under conservative management.

Surgical intervention is indicated if repeated episodes of hemorrhage occur or if the volume of circulating blood cannot be maintained by repeated transfusions of whole blood.

SUBPERITONEAL HEMORRHAGE encountered at operation, or observed at autopsy, has usually been reported as an uncommon and puzzling condition in which loss of blood had not been suspected.

In 1941, after experience with four cases and review of the literature, Cushman and Kilgore[2] described a series of signs and symptoms which it was believed would lead to clinical diagnosis in many instances. The initial symptom of the syndrome is dull, constant abdominal pain, sudden in onset and usually accompanied by nausea. Vomiting aggravates discomfort instead of bringing relief. Continued bleeding increases the intensity of the pain, owing to the gradually enlarging hematoma confined between leaves of a mesentery or beneath visceral peritoneum. There is apprehensive stirring and turning in vain search for a position of comfort. When bleeding stops, the pain gradually subsides, only to return on resumption of hemorrhage, which may be incited by eating, catharsis, retching or effort. Although bleeding doubtless very frequently stops and does not recur, these episodes of subsidence and return of pain, indicative of intermittent bleeding, have been repeatedly noted in reports of cases of proven subperitoneal hemorrhage. Several episodes may occur within a few hours, or the period between them may be several days.

Physical examination early in this phase before peritoneal rupture seldom reveals more than local tenderness without muscle rigidity. Later, if there has been considerable bleeding, the mass of the hematoma (in some locations) may be felt on careful palpation.

Normal pulse and blood pressure often give a false sense of security, even with rapid loss of blood in a short period of time. If hemorrhage is suspected, rapidly raising the patient to an upright position may cause definite increase in pulse and drop in pressure — the earliest objective evidence of acute loss of blood. Determination of the erythrocyte content of the blood and hematocrit estimations are also of little diagnostic value in the first few hours, but are invaluable as a baseline, since progressive anemia is confirmation of the clinical diagnosis.

If recurrences of bleeding are sufficiently far apart, successive drops in erythrocyte content with gradual recovery between incidents supplies dramatic proof of the diagnosis.

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PERITONEAL RUPTURE

If hemorrhage continues, slowly or rapidly, with or without remission, the overlying peritoneum ultimately ruptures. This is heralded by sudden excruciating exacerbation of pain, with shock which is often profound and frequently fatal. If the patient survives this, early abdominal examination reveals diffuse soreness and exquisite rebound tenderness without muscle guarding, which gradually merges into increasing rigidity with distention—the picture of hemoperitoneum with peritonitis and its concomitant adynamic ileus.

The etiologic delineation is that of apoplexy in general. Subperitoneal hemorrhage is twice as common in males, with greatest incidence in those with obvious vascular disease.

Onset is frequently precipitated by trauma or strain—often so minor in character as to seem insignificant. The source of bleeding is a branch of the superior mesenteric artery in nearly 75 per cent of cases.

The previously mentioned report on this condition,[2] published in 1941, was based on 22 cases—too few for statistical evaluation. The author now has reviewed data on 49 additional cases, including four personally observed, a total of 71, to assess the validity of description of the condition as a syndrome and to evaluate treatment.

TABLE 1.—*Classification of 71 Cases of Subperitoneal Hemorrhage*

	Total Cases	Average Duration of Symptoms (days)	Subsidence and Recurrence	
			Cases	Per cent
Operation				
Hematoma	18	3.1	6	28
Hemoperitoneum	30	10.0	15	50
No Operation				
Died	16	19.5	9	56
Recovered	7		4	59

Fifty of the 71 patients were male. Obvious vascular disease was present in 42 per cent, and history of trauma or strain was noted in 18 per cent (and probably would have been found in many more with meticulous inquiry).

Subsidence and recurrence of pain, progressive anemia, the appearance of a mass and secondary collapse imply sufficient duration of time to permit of recognition of these phenomena. Since the period of observation in these cases was terminated by operation in some instances and by either death or ultimate recovery without operation in others, they have been divided into four groups (Table 1).

Patients in the first and second group were operated upon in the hematoma and the hemoperitoneum phases, respectively. The third group was made up of patients who died without surgical intervention, and the fourth of those who recovered without operation. The average duration of symptoms was three days in the first group, ten days in the second, and 19 days in the group of those that died. No attempt was made to calculate duration of time before diagnosis in those who recovered.

The proportion of cases in which history of subsidence and recurrence of pain was obtained was in direct ratio to the duration of symptoms—28 per cent in the first group, 50 per cent in the second, 56 per cent in the third, and 59 per cent in the cases in which there was spontaneous recovery.

Erythrocyte count, hemoglobin value or hematocrit estimation was recorded in only 39 of the cases, and was repeated in but 13. The erythrocyte content when first determined was above 4,000,000 cells per cu. mm. in 18 cases (46 per cent), and less than 3,000,000 in six cases (15 per cent). Progressive loss of blood was demonstrated in all of the 13 cases in which repeated counts were made.

A palpable mass was recorded in eight cases. In 75 per cent of those patients known to have free blood in the abdomen, the onset could be identified by sudden increase in pain followed by collapse.

It seems evident that these signs and symptoms are quite constant in a substantial percentage of cases (Table 2), and that the syndrome of subperitoneal hemorrhage can lead to clinical diagnosis provided the possibility of bleeding is considered.

Diagnosis was made clinically in only four of the cases in which operation was done and in none of the cases in which the patient died without operation. Seven cases were diagnosed and the patients treated expectantly without mortality.

Active bleeding at operation was encountered in eight cases and was controlled by pack in two and by ligation in six, with one death. In eight cases resection or exteriorization was performed to prevent recurrence of bleeding, with two deaths. No active bleeding was found and no definitive operation was carried out in the remaining 32 cases, in 12 of which the patient died. The mortality rate for all cases in which operation was done was 32 per cent.

It is obvious that, contrary to general opinion, spontaneous recovery does occur and that operation is not the only method of treatment.

Failure to establish diagnosis led to unnecessary operation in many cases, and in others prevented adequate blood replacement and opportune operative intervention that might have been successful.

If the diagnosis of subperitoneal hemorrhage can be made, there is adequate time in most instances to replace lost blood. In many cases bleeding may cease and not recur, making operation unnecessary.

If it becomes apparent that operation is inevitable, either because of repeated episodes of hemorrhage or failure to maintain blood volume despite repeated transfusions, the chance of successful intervention is greatly enhanced by adequate preparation for definitive surgical procedure.

Presence of hemoperitoneum in itself is not an indication for operation. Attention should be directed toward bringing attendant shock under control. When that is done, it may be apparent that bleeding has ceased.

Surgical treatment of subperitoneal hemorrhage is a formidable operation since it frequently requires bowel resection—no simple procedure in the face of massive hematoma or hemoperitoneum. Discovery of an active bleeding point is fortuitous, seldom occurs, and should not be expected.

It is impossible to estimate the proportion of cases in which operation will be necessary, but personal

TABLE 2.—*Incidence of Signs and Symptoms in Cases of Subperitoneal Hemorrhage*

	Per cent
Vascular disease	64
Trauma or strain	18
Palpable mass (eight cases)	11
Subsidence and recurrence of pain	46.5
Initial evident anemia	54
Progressive anemia	100
Sudden collapse with hemoperitoneum	75

experience with eight patients, three subjected to exploration without definitive operation and the remaining five treated without operation, leads the author to believe that spontaneous recovery is the rule rather than the exception.

CASE REPORTS

CASE 1 (Reported through the courtesy of Dr. C. E. Smith): A woman 40 years of age was admitted to St. Joseph's Hospital with history of constant abdominal pain of five days' duration. The next day pain was centered in the right lower quadrant of the abdomen. It was not severe, but persistent and annoying. There was some diarrhea and finally nausea without vomiting.

The temperature was 99.4° F., the pulse rate 96, and respirations 18 per minute. The hemoglobin value was 91 per cent, erythrocytes numbered 4,860,000 per cu. mm. of blood, and leukocytes 17,400—70 per cent polymorphonuclear cells. The urine contained a few pus cells and there was a trace of albumin.

Upon examination local tenderness was noted in the right lower quadrant without rigidity. No mass was palpable. No abnormality was observed upon pelvic examination. The preoperative diagnosis was subacute appendicitis.

The cecum was delivered through a McBurney incision, disclosing a diffuse subperitoneal hematoma involving the ascending colon as far as it could be visualized and extending into the mesentery of the distal two inches of the terminal ileum. The caput of the cecum and the appendix were normal. The appendix was removed and the abdomen closed without disturbing the hematoma. The postoperative course was uneventful, and the patient was discharged on the fifth postoperative day.

It was later learned that the patient had been struck in the abdomen shortly before the onset of pain.

CASE 2 (Reported through the courtesy of Dr. G. D. Delprat): A 57-year-old man became nauseated and diarrhea developed concomitantly with continuous abdominal pain which subsided and recurred at intervals for four days. He then suddenly collapsed while eating in a restaurant and became unconscious. Taken to an emergency hospital for treatment of shock, he was later transferred to St. Luke's Hospital.

The blood pressure was 139 mm. of mercury systolic and 98 mm. diastolic. The erythrocyte content in the blood was 4,000,000 per cu. mm. and the hemoglobin value 67 per cent. Leukocytes numbered 19,200—80 per cent polymorphonuclear cells. The urine contained casts and the reaction for albumin was 4 plus.

There was pronounced tenderness throughout the abdomen with rigidity over the entire epigastrium. The peripheral blood vessels were arteriosclerotic.

The next day erythrocytes numbered 3,770,000 per cu. mm. and the hemoglobin value was 62 per cent.

The day following, the abdomen suddenly became boardlike. A diagnosis of carcinoma of the bowel with perforation and beginning peritonitis was made and operation was carried out. When the abdomen was opened, about one pint of dark red free blood was encountered and the transverse colon was observed to be gangrenous. The bowel was rapidly exteriorized and the patient was returned to the ward in poor condition. He died the next morning.

Thrombosis of the superior mesenteric artery and a mesenteric hematoma down to the cecum and along the splenic vessels were noted at autopsy.

CASE 3 (Reported through the courtesy of Dr. Wesley Scott and Dr. Martin Debenham): A woman, 28 years of age, was admitted to St. Joseph's Hospital with complaint of lower right quadrant abdominal pain which started suddenly as she arose from a chair four hours before admittance to hospital. The pain was constant in character but had gradually increased in severity. There had been no nausea or vomiting. There were 3,960,000 erythrocytes per cu. mm. of blood and the hemoglobin value was 73 per cent. Leukocytes numbered 13,050 per cu. mm. Upon physical examination localized tenderness without rigidity was noted in the right lower quadrant of the abdomen.

The preoperative diagnosis was acute appendicitis. Upon operation the appendix was found to be essentially normal and in further exploration a hematoma was observed in a pedunculated lipoma of the parietal peritoneum near the upper end of the incision. This was ligated at the base and removed. The postoperative course was uneventful. There was no evidence of vascular disease at that time or upon reexamination some five years later.

CASE 4 (Presented through the courtesy of Dr. Gilbert M. Barrett): A 65-year-old housewife was admitted to St. Luke's Hospital with complaint of weakness, nausea and constant girdling pain around the abdomen of a week's duration. The patient had vomited once two days before entry. Twenty-four hours later pain developed suddenly on the right side of the abdomen and was still present.

The pulse rate was 60 and the blood pressure 74 mm. of mercury systolic and 58 diastolic. Erythrocytes numbered 2,700,000 per cu. mm. of blood and the hemoglobin value was 54 per cent.

There was pronounced generalized tenderness of the abdomen. A mass was palpated in the right side, slightly higher than the cecum. No abnormality was noted roentgenographically with barium enema. In intravenous pyelograms there was evidence of displacement of the ascending colon to the right. The tentative diagnosis was malignant disease, and transfusions of whole blood were started in preparation for operation.

The pain gradually disappeared, then recurred on the tenth hospital day. Again it subsided, and on the fifteenth day returned. Once more it subsided and the patient was quite comfortable again, but shock developed suddenly on the seventeenth day and the patient died.

At autopsy a large amount of free blood was observed in the peritoneal cavity. It had come from a ruptured laminated hematoma in the mesentery of the terminal ileum. Minimal arteriosclerosis was noted in examination of the heart and blood vessels.

Following is the record of erythrocyte determinations and of transfusions of whole blood:

Day	Erythrocytes per cu. mm.	Transfusion
First	2,700,000	500 cc.
Third	2,700,000	500 cc.
Fifth	2,300,000	500 cc.
Twelfth	2,100,000	500 cc.
Fourteenth	.....	500 cc.
Sixteenth	.....	500 cc.
Seventeenth	1,900,000	

CASE 5 (Reported through the courtesy of Dr. E. L. Bormann): A 6-year-old girl was admitted to the Palo Alto Hospital, January 16, 1949. Thirty-six hours before entry aching pain had developed in the abdomen and it had gradually increased. There had been no nausea or vomiting, and no bowel movement for 24 hours. The family stated that the patient had been kicked in the abdomen by her four-year-old brother two days before but had complained only a little

at the time. The temperature was 99.6° F. and the pulse rate 96.

There was slight abdominal distention, tenderness and rigidity in the right lower quadrant, and mild rebound tenderness referred to the right lower quadrant. Leukocytes numbered 16,000 per cu. mm. of blood. The urine was normal.

Five hours later the local signs had increased. The provisional diagnosis was appendicitis or mesenteric adenitis. The abdomen was entered through a McBurney incision. The appendix and mesenteric glands were normal. A mass felt in the upper right quadrant was delivered into the wound and was observed to be a 7x4x1 cm. infarct of the omentum. It was resected and the abdomen closed. Convalescence was normal and the patient was discharged on January 21, 1949.

The pathologist's report was: "Extensive hemorrhage along the fascial planes and around small blood vessels. A single vessel shows thrombosis with partial recanalization."

CASE 6 (Reported through the courtesy of Dr. Ruth Fleming): A 15-year-old boy was admitted to St. Joseph's Hospital February 20, 1952, about eight hours after an automobile accident. About two hours before entry he had received sedation for severe pain at an emergency hospital and was semi-conscious on arrival, but could be roused. The temperature was 96.6° F., the pulse rate 112, and respirations 24 per minute. The blood pressure was 90 mm. of mercury systolic and 60 mm. diastolic.

The patient was pale, perspiring, and obviously in shock. There were large bruises over the right hip and the lower ribs on the right side. The only abnormality noted in neurological examination was that the pupils of both eyes were small and did not respond to light. The lungs were clear and expansion was equal. The abdomen was slightly distended but soft to palpation. No masses were felt. There was no audible peristalsis.

There were 4,500,000 erythrocytes per cu. mm. of blood and the hemoglobin value was 80 per cent. Leukocytes numbered 52,000 per cu. mm.—97 per cent polymorphonuclear cells. The cell volume was 33 per cent of the whole blood. Blood was visible in the urine.

The patient was given 500 cc. of whole blood as soon as typing and cross matching could be carried out. The pulse rate promptly decreased and the blood pressure increased. During the first two hours the patient vomited about 400 cc. of "coffee-ground" material.

Upon repeated abdominal examinations some rigidity of the right abdominal wall and tenderness to palpation were noted. The patient complained of abdominal pain, which was relieved by codeine. Abdominal peristalsis was demonstrated and no evidence of free air was observed in a plain film of the abdomen. There was no further vomiting. The tentative diagnosis was retroperitoneal hemorrhage.

The patient was permitted to take fluids by mouth on the second hospital day and food on the third. The abdominal pain gradually subsided and a mass was palpable in the right subcostal area. On the fifth hospital day, after two days in which there was no discomfort, steady pain again developed in the right side and it was necessary to give codeine for relief. The pain gradually diminished and the patient was permitted to sit up on the twelfth day. He soon became nauseated, however, and once more there was dull pain on the right side for a short time. Convalesence thereafter was rapid and uneventful. The patient was dismissed on the seventeenth day, and two months later was still well.

A record of erythrocyte determinations, hematocrit readings and transfusions of whole blood follows:

Date	Erythrocytes per cu. mm.	Cell Volume (per cent of whole blood)	Transfusions
Feb. 20, 1952	4,500,000	33	500 cc.
Feb. 21, 1952	3,600,000	33	500 cc.
Feb. 22, 1952	.....	34	.....
Feb. 23, 1952	2,870,000	27	500 cc.
Feb. 24, 1952	.....	39	.....
Feb. 25, 1952	.....	32.5	.....
Feb. 26, 1952	3,640,000	37	.....
Feb. 27, 1952	.....	40	.....
March 1, 1952	4,000,000	39	.....
March 3, 1952	3,600,000	36	.....
March 6, 1952	4,380,000	40	.....

CASE 7: The patient, a 30-year-old woman, was observed in consultation with Dr. L. Parry Douglass.

At about 1 p.m. the patient became aware of a dull pain in the epigastrium. It was localized and steady, with few remissions, and gradually increased in intensity. At 6 p.m. the pain, then moderately severe, was localized in both upper quadrants of the abdomen. Two hours later there was unbearable pain over the entire abdomen and radiating to the back. The patient took three glasses of baking soda and water, administered an enema, and then induced vomiting. This gave transient relief, but the pain returned suddenly with even greater intensity and the patient was admitted to St. Joseph's Hospital.

The patient said that menstruation was regular and normal and that the last period had ended five days previously. The temperature was 99.6° F., the pulse rate 92 and respirations 22 per minute. The blood pressure was 104 mm. of mercury systolic and 62 mm. diastolic.

There was diffuse generalized tenderness over the entire abdomen with moderate muscular guarding and exquisite rebound tenderness. The peristaltic sounds were normal to auscultation. No shifting dullness was elicited on percussion. Results of pelvic examination were normal. A plain film of the abdomen was reported to show a "moderate amount of gas in the large bowel and some slightly dilated loops of small bowel in the left flank, possibly due to an early ileus or obstruction." Erythrocytes numbered 4,100,000 per cu. mm. of blood. The hemoglobin value was 78 per cent. Leukocytes numbered 9,200 per cu. mm.—82 per cent neutrophils. The urine was normal.

The tentative diagnosis was hemoperitoneum due to rupture of hematoma, source undetermined.

The patient was given sufficient medication to control pain and ingestion of liquids was restricted. The next day the observations upon physical examination were essentially the same as before except for slight increase in abdominal distention. Since liquids were well tolerated by mouth, restriction was discontinued. On the third day the patient moved more freely in bed but would not turn on her side. The physical findings remained the same. Later in the day the patient complained of pain in the left shoulder.

Fluoroscopio examination on the fifth day showed some limitation of motion of the left dome of the diaphragm without elevation. There was a large amount of gas in the colon.

Throughout this time pronounced tenderness and rigidity of the abdomen persisted, and the pain in the left shoulder, while not as acute as when first noted, was still present. The peristaltic sounds of the abdomen were of normal pattern, and although there was slight distention the patient passed flatus and a loose stool. No abnormality was noted in repeated vaginal examinations. All symptoms and objective findings gradually subsided. As the patient improved,

tenderness and spasm lingered in the left side below the ribs. In a roentgen study with barium enema on the fourteenth hospital day, moderate spasm of the sigmoid colon was noted. Sigmoidoscopic examination was carried out and the mucosa was observed to be normal. Erythrocyte determinations after the first day were as follows: Second day, 4,500,000 per cu. mm.; third day, 3,720,000; fifth day, 3,990,000; fourteenth day, 4,700,000.

The patient was discharged from the hospital on the sixteenth day with slight residual tenderness in the left side which soon abated. There was no recurrence in eight months.

CASE 8 (Referred by Dr. Walter Kollman): A 55-year-old fireman was admitted to St. Joseph's Hospital with complaint of severe upper abdominal pain. He had been awakened about 4 a.m. by constant severe discomfort in the epigastrium which he attributed to indigestion induced by a heavy meal the evening before. He was nauseated but did not vomit. After the patient had sat up awhile rubbing his abdomen the pain gradually diminished and he was able to fall asleep. Two hours later he was again awakened by recurrence of pain more severe than before.

The temperature was 99° F., the pulse rate 84, and blood pressure 190 mm. of mercury systolic and 106 mm. diastolic. The erythrocyte content of the blood was 5,070,000 per cu. mm. and the hemoglobin value 110 per cent. Leukocytes numbered 17,300 per cu. mm.—92 per cent polymorphonuclear cells.

Upon examination of the abdomen (fifteen hours after onset of pain) moderate muscle rigidity and some distention were noted. There was quite pronounced diffuse tenderness to palpation, most evident in the epigastrium. Upon auscultation the peristaltic sounds were noted to be few and faint.

The pain seemed to have become somewhat colicky in character, and operation was advised upon a tentative diagnosis of mesenteric thrombosis. When the peritoneum was opened, approximately 500 cc. of dark red blood was evacuated. The small bowel was distended and inflamed. In careful examination of the full length of the bowel no evidence of obstruction was noted. The pancreas seemed slightly indurated but there was no evidence of fat necrosis. The mesentery of the bowel did not contain a hematoma and no source of bleeding was found. The abdomen was closed and the patient was returned to his room in fair condition with indwelling intestinal suction which continued for three days. The distention subsided and normal peristalsis returned. Convalescence was uneventful and the patient was discharged on the twelfth hospital day. He had no recurrence of symptoms.

CASE 9: A 29-year-old housewife entered St. Joseph's Hospital on January 2, 1949. She had been struck beneath the right costal margin during a New Year's Eve brawl. The blow was hard enough to "knock the wind out of me" but had no other immediate effect. About two hours after retiring, she was awakened by constant and gradually increasing pain in the region where the blow had landed. She became nauseated and vomited repeatedly without relief. Pain subsided to a dull ache the next day but recurred in greater severity on the morning of entry.

Erythrocytes numbered 3,010,000 per cu. mm. of blood, and the hemoglobin value was 63 per cent. There were 12,000 leukocytes per cu. mm.—91 per cent neutrophils. Results of urinalysis were within normal limits.

The only abnormality noted upon physical examination was pronounced diffuse tenderness in the upper right quadrant of the abdomen, without muscle spasm. The chest and abdomen were roentgenographically normal.

The tentative diagnosis was subperitoneal hemorrhage. Ingestion of fluids was discontinued and the fluid balance was maintained by parenteral injection. Typing and crossmatching of the patient's blood was carried out and the house staff was alerted to the possibility of sudden collapse and need for therapy to overcome shock.

Nausea and vomiting promptly ceased and pain gradually diminished. Three days after the patient was admitted, a tender mass which did not move with respiration could be palpated in the upper right quadrant of the abdomen. A soft diet was started on the fourth hospital day. Convalescence was uneventful and the patient was discharged January 17. When the patient was last examined, two months later, the mass was still palpable, but less definite. She was reported to have remained well.

Data on erythrocyte determinations and transfusions of whole blood follow:

Day	Erythrocytes per cu. mm.	Transfusions
Jan. 2	3,010,000	.....
Jan. 3	2,910,000	500 cc.
Jan. 5	3,020,000	500 cc.
Jan. 6	3,910,000	.....
Jan. 17	4,760,000	.....

CASE 10: A 46-year-old man slipped while working on a step ladder. As he fell a metal extension struck him in the abdomen on the left rectus muscle, causing severe immediate pain which diminished to a dull ache. He finished his work without difficulty but three hours later, after he had eaten dinner, the pain gradually increased in severity. It was constant in character and soon caused nausea and vomiting which gave no relief. The patient was admitted to St. Joseph's Hospital eight hours after injury. At the time of admittance the patient seemed apprehensive and obviously was in severe pain which prevented his remaining still. The temperature was 97.8° F., the pulse rate 52, respirations 18 per minute, and the blood pressure 122 mm. of mercury systolic, and 90 mm. diastolic.

The abdomen was soft to palpation, with localized tenderness to the left of the umbilicus. Contraction of the recti caused no change in the pain. Bowel sounds were normal.

No evidence of free air was observed in an x-ray film of the abdomen and the gas pattern appeared to be normal. The shadow of the right psoas was sharp and distinct but there was a bulging haziness in the lower half of the left psoas. The roentgenologist interpreted this as evidence of possible hemorrhage into the left psoas muscle. The tentative diagnosis was subperitoneal hemorrhage. All oral intake was stopped. Codeine, 0.06 gm., with sodium phenobarbital, was given intramuscularly. The pain was relieved, and eight hours later the patient was given fluid by mouth, starting with 1000 cc. of 5 per cent glucose in normal saline solution to restore fluid balance. A soft diet was instituted with six feedings a day. There was no recurrence of pain. The abdomen remained soft and flat and local tenderness gradually diminished. The patient was dismissed from the hospital on the fourth day and was discharged from further care, asymptomatic, two weeks later.

Laboratory data on examinations of the blood were as follows:

Day	Erythrocytes	Leukocytes	Hematocrit
Day of admittance (11 p.m.)	5,410,000	23,500 (95% neutrophils)	.....
First morning	5,000,000	.....	.....
afternoon	4,690,000	20,000	38 mm.
Second	4,820,000	.....	.....
Third	4,760,000	.....	47 mm.

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Shipment of "Cancer Diagnosis Kit" Enjoined

FOOD AND DRUG ADMINISTRATION has obtained a permanent injunction against the William Dunkler Laboratories, Chicago, to stop shipments of Dunkler's cancer diagnosis kit. Dr. Gordon Granger, FDA medical officer, commented: "The danger to public health of this scheme for cancer detection is emphasized by the fact that . . . tests showed negative results in 59 of 76 cases known to be malignant."—*From the A.M.A. Capitol Clinic.*

Moles, Melanomas and Epitheliomas in Children

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• The management of moles which occur in childhood is important from the standpoint of clinical diagnosis and treatment. Melanomas of both the malignant and juvenile types are sometimes mistaken for ordinary moles. Malignant epithelial tumors are rare in childhood as are congenital tumors. There is a possible relationship between congenital defects of various types and childhood neoplasms.

THE PURPOSE of this presentation is to briefly consider the practical management of pigmented nevi in childhood. Such a discussion must necessarily include the problem of juvenile melanomas. In addition, the occurrence of cutaneous malignancy in this age group will be briefly discussed.

First, as to a classification of so called pigmented nevi:

TYPES OF PIGMENTED NEVI

1. *Epithelial, intra-epidermal or acanthotic nevi* frequently occur as linear lesions with segmental or metameric distribution. They may also appear as verrucous, raised, solitary lesions. Usually they are present at birth, and while pigment may be present or absent, such a lesion is not important as a precursor of malignant melanoma. It may be the site of a prickle cell carcinoma in later life, however.

2. *Junction nevus* is a term applied to any pigmented lesion having active proliferating nevus cells at the dermo-epidermal junction. Most so-called pigmented moles in children either are of this type or have at one time had so-called junctional activity. Lund[12] as well as Montgomery and Stegmaier[26] in studies on pigmented moles in early childhood observed that such junctional changes occurred in all such lesions. Clinically the pure junction nevus is non-hairy, smooth, flat or macular and light brown, dark brown, blue or black. The commonest sites are the face, lower extremities and genitalia.

Junctional activity in association with definite nests, bands or strands of nevus cells in the cutis is not uncommon in this age group.

3. *Intradermal, intracutaneous, dermal or cutis nevus.* These synonymous terms are applied to pigmented nevi in which the nevus cells are confined to the dermis. Purely dermic nevi are uncommon in infancy and early childhood. The incidence increases in the prepubertal years. This is because the nevus cells in the cutis derive from the proliferation of nevus cells at the dermo-epidermal junction. Hence the cutis nevus represents a more adult or differentiated type of pigmented growth than the junction nevus from which it derives. Not infrequently some junctional activity is found in such lesions. However, true dermal nevus, a precursor of malignant melanoma, is exceedingly rare. Clinically these lesions are usually soft to firm, brown, elevated, smooth or slightly papillomatous. They may or may not contain hairs.

4. *Blue nevus* is frequently mistaken for a malignant melanoma because it occurs as a blue to blue-black, non-hairy, firm, elevated, circumscribed nódule or tumor. Varying in size from 5 to 15 mm. in diameter, its surface is usually smooth. A presumptive clinical diagnosis is only possible when such a lesion has existed without change from early childhood. Simple excision is adequate therapy. The histologic structure is quite characteristic. Malignant degeneration is extraordinarily rare and (as far as the author could determine) has not been reported in childhood.

5. *Mixed, combined or compound nevus.* This term is usually applied to a lesion which has histologic features of both the dermal nevus and the junction nevus. However, it also can be applied to the rare combination of a deep blue nevus and an overlying dermal nevus. The author does not recall ever having seen an epithelial nevus combined with a junction, dermal or blue nevus, although Montgomery[14] stated that "linear nevi with or without pigment may contain nevus cells."

SPONTANEOUS DISAPPEARANCE OF PIGMENTED NEVI

For two reasons the author takes exception to the statement that pigmented nevi never disappear spontaneously.[13] First, unpublished personal observations have led to certainty that the phenomenon of leukoderma centrifugum acquisitum of Sutton represents spontaneous cure of an ordinary pigmented mole.

Second, in microscopic study of all soft, pedunculated, flesh-colored, fibromatous lesions removed

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from adults, it was noted that a surprising number contained greater or lesser numbers of nevus cells with variable amounts of fibrous connective tissue. Pigment was absent. Rarely, small foci of junctional activity were present. However, all gradations as to the numbers of nevus cells in the dermis were observed. It is hard to avoid the conclusion that the end stage of some pigmented nevi is fibrosis.

JUVENILE MELANOMA

There is a rare type of melanoma occurring in childhood which deserves special consideration. Great credit must be given to Spitz[25] who collected data on a group of 13 such cases and established the disorder as a definite clinical and pathologic entity.

Clinically the condition is a solitary lesion seldom larger than 1 cm. in diameter. This lesion is not infrequently a firm, flesh-colored or slightly pink nodule definitely elevated above the surface of the skin. It may, however, be brown or black, but is probably never hairy. In only one of the four cases of which the author has personal knowledge was there evidence of pigmentary disturbance—three separate and distinct brown pinhead-sized macules, one of them at the very edge of the lesion and the other two in apparently normal skin a millimeter distant from the visible edge of the nodule.

The histologic structure of lesions of this kind is such as would occasion alarm if the patient were an adult. There is pronounced cellular activity at the dermo-epidermal junction. The proliferating cells, which vary widely in size, produce melanin. They are larger than the cells of the epidermis and may be fusiform, round or polyhedral. Quite characteristic are large bizarre mononuclear or multinuclear giant cells.

TREATMENT OF MOLES

Slaughter[22] made the following statement: "There is considerable mythology and misunderstanding about the treatment of moles. There is much popular fear that disturbing a mole in any way may be dangerous. In my personal experience and in the literature, there is no authenticated instance of a benign neuronevus becoming malignant after incomplete removal with the electric needle, cautery or excision. Close scrutiny of such supposed occurrences will almost invariably show that the mole was malignant in the first place and usually treatment was instituted because of the changes incident to unrecognized malignant transformation. Dermatologists have removed thousands and thousands of moles with acid, carbon dioxide snow, electrocautery and so forth, without untoward occurrence. Removal of moles on the face for cosmetic reasons by these methods would seem to be perfectly safe."

Slaughter went on to point out that there are two disadvantages to such a procedure: (1) There is no tissue for microscopic section and (2) there is usually incomplete destruction of such a lesion. These objections, however, can be overcome by Becker's method of removing the upper two-thirds of the lesion with scissors for histologic study, then destroying the remainder of the lesion by electrodesiccation. An excellent cosmetic result is usually obtained.

MALIGNANT MELANOMAS IN CHILDHOOD

Spitz[24] disputed Montgomery's[14] statement that malignant melanoma is more frequent among children than other types of epithelioma. Nevertheless, malignant melanomas do occur in childhood and various observers have reported one or more cases.[4, 11, 14, 24] It is to be noted that malignant transformation may take place in so-called hairy moles[14] and especially in the giant hairy nevi sometimes called "bathing trunk nevi."

CARCINOMA OF THE SKIN IN CHILDHOOD

The most important condition predisposing to carcinoma of the skin in childhood is xeroderma pigmentosum.[3] This condition frequently occurs in children whose parents are blood relatives. The manner of inheritance has been studied extensively. At one time consideration was given to the possibility of partial sex linkage with transmission of the disease through the X or Y chromosome. Results of recent genetic studies, however, seemed to indicate that the disease is transmitted by simple recessive genes.

From a dermatologic standpoint the condition starts early in life and on areas exposed to sunlight, to which there is an abnormal sensitivity. Clinical features are pronounced freckling or pigmentation with erythema and telangiectasia followed by the development of scaling hyperkeratotic lesions along with atrophic depigmented areas and considerable conjunctival hyperemia. In the course of a few years carcinoma develops, particularly on the face or conjunctiva. These cancerous lesions are usually multiple and may be of the basal cell type, in which case the lesion is often pigmented. Frequently the lesion is prickle cell carcinoma. The occurrence or development of malignant melanoma and fibrosarcoma, while uncommon, has been reported. The condition is exceedingly serious and usually leads to early death.

There are clinical signs and familiar factors by which it is possible to determine that a given person

probably is a carrier of the recessive genes involved in inheritance of this disease.[15] Heavy freckling in one or both of the parents or in brothers or sisters of a patient with xeroderma pigmentosum is extremely strong evidence that any of them, if not actually having a mild form of the disease,[1] is a carrier of the recessive gene.

Aside from xeroderma pigmentosum, there is another group of malignant epithelial growths of a kind that arise in a preexisting nevus. They are not, however, to be confused with pigmented moles. A nevus of this type is usually a unilateral,[18] sometimes linear birthmark. Its histologic structure may be epidermal and acanthotic, or it may be made up of sebaceous cells, as is the nevus sebaceus of Jadassohn.[19] Sometimes the nevus, like nevus syringocystadenoma papilliferus, is composed of sweat gland cells.

The carcinomas arising from such nevi are usually of the malignant prickle cell variety, but basal cell epitheliomas have been reported. Actually such malignant changes for the most part occur in adult life, but may occur in childhood. The author observed one case of prickle cell epitheliomas which developed on a sebaceous nevus in a girl eight years of age.

BASAL CELL EPITHELIOMA

There is a very rare group of multiple congenital basal cell epitheliomas, examples of which have been reported by Nomland[17] and Nisbet.[16] The lesion in the case reported by Scharnagel and Pack[20] probably belongs in this group. In early life these lesions are indistinguishable from flat pigmented nevi.

CALCIFYING EPITHELIOMA (MALHERBE)

Calcifying epithelioma (Malherbe) occurs in children most often on the face, neck and upper extremities. It is a solitary, subcutaneous, hard, deep-seated tumor from 1 to 3 cm. in diameter covered by normal skin. The diagnosis must be made on the basis of the histologic structure, which is said to be characteristic. Nevertheless it is only fair to state that some investigators[27] hold to the belief that such lesions are calcified epidermal cysts, a view with which the author is inclined to agree.

CONGENITAL TUMORS

A wide variety of congenital tumors involving the skin or mucous membranes have been reported. These are of several types. In some instances the condition is inherited, as in Recklinghausen's neurofibromatosis.[21] In other cases benign congenital tumors of the gum have occurred.[10, 23] In still another group, congenital malignant tumors of the thymus with extensive cutaneous metastases have been reported.[2,8, 28]

Finally, a rare occurrence is the birth of a baby with malignant tumor resulting from the fact the mother had generalized metastatic carcinomatosis or melanomatosis during pregnancy and the disease was transmitted via the placenta to the fetus.[7, 9]

CONGENITAL DEFECTS

The possible relationship between congenital defects of various types and various neoplasms occurring in childhood has been discussed by Dargeon.[5, 6] Congenital malformations such as supernumerary digits, cataracts, hemangiomas and developmental abnormalities of the heart have been associated with such neoplasms as Wilms' tumor, rhabdomyosarcoma, lymphosarcoma and astrocytoma of the cerebellum.

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A Curb on Excessive Fees

HARTFORD (CONNECTICUT) COUNTY'S 867-member medical society recently adopted a new by-law which is aimed at curbing doctors who try to saddle patients with exorbitant charges.

The Hartford *Times*, reporting the society's action, said:

"The move is another step by the public relations-conscious organization to strengthen the position of the profession with the public by imposing shackles on any who might tear down public confidence through gross overcharging. It is believed to be the first of the state's eight county medical societies to give its officials such broad powers."

The newspaper said that the county society amended its by-laws to give the committee on medical ethics and deportment a strong weapon to "police" its ranks in matters of overcharging.

One provision of the by-law is that the committee can call in three impartial doctors who are specialists in the field involved and get their advice on the reasonableness of fees for service given.—*From the A.M.A. Secretary's Letter.*

Early Diagnosis of Malignant Melanoma of the Skin

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• About five per cent of all malignant lesions of the skin are malignant melanomas. The poor prognosis associated with this malignant lesion emphasizes the importance of early diagnosis. A large proportion of malignant melanomas arise in preexisting lesions such as junction nevi, precancerous melanoses and, much more rarely, blue nevi. Early malignant changes in these precursor lesions include increasing pigmentation, enlargement, thickening, crusting, bleeding, ulceration, tumor formation, and development of satellite lesions.

Many pigmented, and some non-pigmented, lesions of the skin must be differentiated from malignant melanoma. Since even with radical surgical treatment the prognosis of malignant melanoma is poor, junction nevi which are subject to continual trauma or have signs of probable malignant degeneration should be prophylactically excised.

PRIMARY MALIGNANT MELANOMA occurs most frequently in the skin and adjoining mucous membranes, next most frequently in the eye and least frequently in the meninges. Primary occurrence elsewhere is very doubtful, and in any case is conceded to be extremely rare. Malignant melanoma constitutes approximately 5 per cent of all malignant lesions of the skin.[6] In the skin of the lower extremities, however, more than 50 per cent of all malignant tumors are melanomas.[3, 9] Because of this relative frequency and the high degree of malignancy and poor prognosis, malignant melanoma is a continuing challenge.

The authors recently studied 454 cases of clinically diagnosed malignant melanoma to determine which clinical and histopathological factors might be used in an earlier and more certain diagnosis. This presentation summarizes the clinical factors which appeared, in study of these cases and of the extensive literature, to be of value in diagnosis. The statistical and histopathological findings from the study will be reported elsewhere.[2]

Most observers agree that the melanoblast, from which the malignant melanoma develops, is found only in the skin, the mucocutaneous junctions, the conjunctiva, iris, retina and choroid of the eye and the leptomeninges. It is now quite certain that most, if not all, malignant melanomas develop from preexisting lesions. At least as far back as 1857 pigmented nevi were definitely pointed out as precursors of malignant melanomas.[10]

Suggestions were made from time to time as to which type of mole, nevus or birthmark was most likely to become malignant, but these suggestions were nearly always wrong. Not until quite recently has it become clear which type of nevus most frequently gives rise to malignant melanoma.

PRECURSOR LESIONS

The precursor lesions of malignant melanomas of the skin are, in order of importance, the junction nevus, the precancerous melanosis and lentigo maligna, the junction compound nevus and the blue nevus. It is evident that the recognition and proper evaluation of these antecedent lesions are of paramount importance in arriving at an early diagnosis and prompt start of prophylactic treatment of malignant melanoma.

The junction nevus, so called because nevus cells are found at the junction of the dermis and epidermis, was named by Sattenstein, the name being later popularized and clinically interpreted by Traub and Keil.[12] The most common pigmented nevus, at least in the first three decades of life, is a light brown to jet black macular lesion, sometimes slightly elevated in the center. The surface is nearly always smooth, occasionally granular, and is free of coarse hair. The size varies from less than 1 mm. to more than 1 cm., but nearly all junction nevi are between 2 and 5 mm. in size. They may be found anywhere on the skin, including the mucocutaneous areas, and occur in all races. The average number found in a patient is said to be about twenty. The authors conclude from their studies that this estimate is probably too low, having actually counted as many as 640 clinically typical junction nevi in one adult patient.

Lentigo appears to be an early form of junction nevus, always smooth and macular, often occurring in great numbers, and microscopically identical with the junction nevus except that the nevus cells do not tend to occur in clusters or theques and are all intra-

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epidermal. Lentigo apparently has less tendency to become malignant than has the typical junction nevus.

Precancerous melanosis is much rarer than the junction nevus but is much more likely to become malignant. Precancerous melanosis develops in older persons, usually on the face, as a light to dark brown spot which slowly enlarges peripherally until, for instance, it may cover a large part of the cheek. Satellite spots may appear and may become confluent with the first lesion. Malignant change usually does not occur until the melanosis has been present for several years; such change, commonly found at the periphery, is indicated by palpable infiltration and the presence of nodules. The term "lentigo maligna," which is used by some writers as a synonym for precancerous melanosis, has been applied in the past to several different conditions. The authors apply it to a melanoma originating in a lentigo, forming a superficial, intra-epidermal malignant melanoma, usually of slow growth and late metastasis.

The junction compound nevus is microscopically a combination of a junction nevus and a dermal nevus. It is an elevated, firm lesion (rarely soft), usually nodular, rounded or dome-shaped, with a smooth or slightly verrucous surface, often containing dark coarse hairs. A junction compound nevus always has areas of pigmentation. The dermal nevus has nevus cells only in the dermis, while the compound junction nevus has nevus cells also in the epidermis or at the epidermal-dermal junction. The development of a malignant melanoma from a compound junction nevus, is much rarer than from a junction nevus, and probably occurs only when such a lesion is subject to repeated trauma. No cases are known in which it was clearly established that a malignant melanoma arose from a non-pigmented, nodular, purely dermal nevus.

The blue nevus contains spindle-shaped melanoblasts (which are believed to be of mesodermal origin in this lesion), located in the dermis in small or large groups. It is a pale blue to dark blue macular to nodular lesion, usually deep-seated, most commonly seen on the hands, feet, face or buttocks. It is usually slightly larger than a junction nevus of average size. Although a blue nevus rarely becomes malignant, the authors have recently observed a patient in whom a blue nevus of the sole of the foot became malignant and metastasized to the regional inguinal lymph nodes.[1]

EARLY MALIGNANT CHANGES

The earliest signs of the development of a malignant melanoma are usually the changes seen in a junction nevus when it undergoes malignant degeneration. These changes do not always occur in the same order, but most frequently there is first noted a darkening of color in the nevus, then an increase in size or a thickening or elevation of the lesion. Further changes may include crusting, ulceration, bleeding, or the development of a nodular tumor. In other cases there is a spilling of pigment into the adjacent skin, or small satellite lesions may appear close to the original nevus. Still later more distant metastases in the skin or regional lymph nodes may develop, or distant visceral metastases may be noted first. Clinical evidence of malignancy in some junction nevi which have already changed into melanomas is so scant—perhaps only a slight increase in pigmentation and barely palpable infiltration—that they are overlooked when search is made for a primary lesion after metastases have become clinically evident.

In a few cases of malignant melanoma of the skin no precursor lesion is clinically evident. The authors have observed at least two such occurrences in patients who had been under observation for other skin conditions, and in whom amelanotic melanomas developed on the face without grossly visible antecedent lesions. In such instances small groups of nevus cells may be present in the epidermis which are not detectable to the naked eye. These may give rise to a malignant melanoma as readily as a larger aggregate of the same cells. The authors have recently seen a section from a primary melanoma of the foot which was less than 2 mm. in diameter and light brown in color but had already given rise to regional lymph node metastases. The malignant change microscopically evident in the antecedent junction nevus was limited to a single rete peg.

In those cases in which no precursor lesions have been noticed, the malignant melanoma may first appear as a pigmented macular lesion which becomes infiltrated, or as a pigmented or non-pigmented nodule or tumor.

After a precursor lesion begins to undergo malignant degeneration, the various changes indicative of malignancy may follow each other in rapid succession, so that within a period of less than two months a fully developed melanotic tumor with metastases may be present. In other cases, particularly those arising in precancerous melanosis or in lentigo, successive changes may be very slow, and metastases from such a melanoma may not occur for years.

How soon metastases may occur after visible changes first appear in a precursor lesion is illustrated by the case of a patient who had had a flat pigmented nevus on the left side of the abdomen all his life. Three weeks before the authors' examination there seemed to be some increase in pigmentation

and a slight enlargement of the nevus. The lesion was widely excised for biopsy, and then radical excision of a large part of the skin of the abdomen was done by a competent general surgeon. No lymph nodes were palpable at that time, and because of uncertainty as to where regional metastasis might have occurred, no groin or axillary dissections were done. There was no local recurrence of the disease but metastases developed almost simultaneously in the contralateral axillary lymph nodes and in the liver, and the patient died of general metastases within two years of the time he first noticed changes in the junction nevus, despite the fact that adequate excision of the primary tumor was done only three weeks after the initial changes became apparent.

Malignant melanoma may spread in several ways. There may be local extension of the disease, sometimes to a pronounced degree. There may be metastases by way of the lymphatic system to adjacent skin areas and to the regional lymph nodes, from which the dissemination may continue through the lymphatic system or through the bloodstream. Metastases may also occur directly from the primary lesion via the bloodstream, causing early widespread metastases. Probably no other tumor tends to metastasize as early and as widely as malignant melanoma; in some cases almost every organ and type of tissue in the body is involved. The earliest symptoms of malignant melanoma may be those arising from the internal metastases, such as to the brain, lung or pancreas, the primary lesion having been unnoticed. On the other hand, after a primary malignant melanoma has been removed the metastatic lesions may not be clinically evident for decades.[5] A primary melanoma may be without visible pigment (a so-called amelanotic melanoma), and metastases from a pigmented malignant melanoma may also be without pigmentation, although microscopically some areas of melanin deposit can be seen in most of these amelanotic lesions.

Although malignant melanoma may arise at any age, the incidence steadily increases with advancing years, and the prognosis is far better before puberty than in later life because there is less tendency to metastasize,[11] apparently owing to endocrine factors which have not yet been specifically determined. These endocrine factors seem to have an opposite effect in pregnancy, where increased pigmentation of nevi is commonly noted, and where there seems to be an increased susceptibility toward malignant degeneration of junction nevi, with early rapid spread of metastases and unusually poor prognosis.

There is no significant difference in the incidence of malignant melanomas in males and females. No race seems to be exempt from this tumor, although there is a higher incidence of melanoma in the light-skinned races. The incidence in Negroes is about one-third that in Caucasians.[4, 7] Most melanomas occur from the fifth to the eighth decade of life, the peak being reached near the age of sixty. The most common site of malignant melanoma is the lower extremities, next the head and neck, and next the upper extremities. The number found on the feet far exceed the number found on any other comparable area. Melanomas are often diagnosed late in the anorectal area, the vulva and vagina, the mouth, and the mucous membrane of the nose.

Melanin may be found in the urine of patients with malignant melanomas if the elaboration of melanin is high. Sometimes this is of prognostic value. If the primary tumor has been adequately excised and no metastases can be demonstrated, and yet there is a definite steady elimination of melanin via the kidneys, visceral metastasis has occurred. Occasionally melanin production is so marked that general pigmentation or melanosis of the skin and mucous membranes takes place. Melanin phagocytized by the regional lymph nodes from a malignant melanoma has at times led to a mistaken diagnosis of metastatic melanoma when actually no malignant cells were present.

DIFFERENTIAL DIAGNOSIS

There are certain lesions of the skin with which malignant melanoma is commonly confused. It is beyond the scope of this presentation to list all such lesions, but a few are common and important. Probably all forms of pigmented lesion should be considered in the differential diagnosis of malignant melanoma. The most common and important of these is, as previously explained, the flat pigmented junction nevus. At times it is clinically impossible to be absolutely certain of the benign or malignant character of a particular lesion. In such cases surgical removal and microscopic study are necessary, and by this means it is possible to determine, in practically every instance, whether a lesion of this type is still a nevus or has changed to a malignant melanoma.

Other pigmented lesions which are confused with malignant melanoma are compound junction nevi, blue nevi, seborrheic and senile keratoses, pigmented basal cell epitheliomas, pigmented or hemorrhagic sarcomas, subepidermal fibromas, hemangiomas, hematomas, accidental tattoo marks, plantar warts and fixed drug eruptions. Nearly all of these can be quite easily differentiated clinically if the lesion is examined thoroughly, although biopsy may be necessary to diagnosis of pigmented basal cell epithelioma, blue nevus, hemangioma, and hematoma, particularly if the last-named is subungual.

Of the non-pigmented lesions which need to be differentiated the pyogenic granuloma is the most important. It usually has a pink to light red color, and a dark crust from previous hemorrhage may increase the resemblance to melanoma. The lips, the nail folds, and the feet are the sites of predilection for this lesion, but it may appear anywhere, particularly on the face. Usually it appears after trauma or infection, grows rapidly (in days instead of weeks as compared with the melanoma), and bleeds upon slight trauma. Although clinically this lesion can usually be differentiated quite readily, in many cases microscopic examination is necessary to make the diagnosis final.

A non-pigmented malignant tumor, particularly if it is fungating, may be confused with amelanotic melanoma. Papillary or fungating squamous cell carcinoma, especially if it appears on the feet, may be difficult to differentiate clinically. Many non-pigmented melanomas have been mistaken for squamous cell carcinoma, even microscopically, until the metastases clearly revealed the true nature of the tumor.

PREVENTIVE TREATMENT

Authors who have studied large series of patients treated for malignant melanoma differ greatly in their report of the mortality rates and life expectancy in these patients. Pack, Perzig and Scharnagel[8] reported an over-all five-year salvage rate of 9.7 per cent and a 17.7 per cent five-year salvage rate in surgical removal of localized melanomas. In selected cases with very radical surgery such as hemipelvectomy and thoracoscapular amputation, a higher salvage rate can probably be attained. It seems clear, however, that even with the best of treatment and under the most favorable circumstances the prognosis of malignant melanoma in adults is poor. Prophylactic treatment, therefore, becomes important. Since most malignant melanomas develop from junction nevi, the intelligent management of these is an essential part of such preventive treatment.

In the cases observed by the authors, as in all other reported series in which the history of trauma was given consideration, irritation and injury have been suspected to be a frequent initiating cause of malignant degeneration in pigmented nevi. Avoidance of trauma to pigmented nevi, particularly of the junction variety, becomes the first consideration in the preventive treatment of malignant melanoma. Patients should be instructed that picking and scratching pigmented moles is dangerous. Junction nevi which are situated where they must unavoidably be subject to friction or other chronic irritation should be excised. Such locations of chronic traumatization are the feet, the waistline, the brassiere area, the fingers and palms, and the neck and beard area in men. Perhaps the shoulders and scapular area should also be included. Junction nevi on the genitalia should also be excised prophylactically. Any junction nevus which has any of the signs of malignant degeneration previously mentioned should be excised with a good margin for microscopic study. Although it is certainly possible to destroy a junction nevus by various methods, including electrocoagulation, all methods except adequate surgical excision should be condemned. Only with surgical excision is there absolute certainty that the lesion has been completely eradicated, and only by this method is a specimen obtained for histopathologic study. A junction nevus or malignant melanoma may be excised by cautery, but the better cosmetic results and the preservation of a more suitable biopsy specimen make cold dissection preferable.

The treatment of malignant melanoma at present is purely surgical. If the tumor is removed before puberty or is one which developed in precancerous melanosis, local excision is usually sufficient. Radiation treatment has not proved to be adequate for either cure or palliation. The most important single factor in the surgical management of a patient with malignant melanoma is early operation, for which an early diagnosis is a prerequisite.

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Dissimilar Allergic Disease in Identical Twins

A Study of Psychosomatic Aspects

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• Identical twins with bronchial asthma were studied. One had the first attack of the disease in late adolescence, the other not until he was adult.

Both were demonstrated by immunologic means to be sensitive to house dust and certain foods. Yet, of itself, the factor of exposure to a known allergen seemed not enough to precipitate clinical allergic reaction in either of them.

It is believed that emotional stress is accompanied by physiologic changes which facilitate increased reactions to antigenic agents that in normal circumstances would not cause clinical disease.

The twins were widely different with regard to emotional development and in their reaction to situations of stress. In both of them allergic manifestations were associated with periods of emotional conflict.

The dissimilar clinical manifestations of allergy in these identical twins may be explained by differences in personality and therefore in reactions to stress situations.

THE CLINICAL SYNDROME of bronchial asthma is the result of pathophysiologic disturbances in the bronchopulmonary system—edema, hypersecretion, and constriction of smooth muscle. The major etiologic factor is assumed to be an antigen-antibody response; that is, a sensitive subject is exposed to an antigenic material and the lungs are the site of an allergic reaction. The cause-effect relationship is not always so clear-cut in individual patients. Exposure to a known antigen may result in clinical asthma under one set of circumstances, but not under another. It may be impossible to link clinical asthma with seasonal incidence of pollen, ingestion of certain foods, or a particular place of residence. Consequently, in recent years many workers have sought to elucidate other factors which, in a susceptible person and in certain circumstances, might combine to produce the clinical syndrome of asthma.

Emotional stress is one such factor which, in combination with a physiologic predisposition, may precipitate an allergic reaction. This association of emotional stress and precipitation of allergic reaction has been demonstrated in the laboratory by Holmes,[10, 11, 12] Wolf and co-workers,[19] Graham,[8] and Treuting[18] and has been commented on by many clinical observers.[1, 3, 5, 7, 13, 15] It should be emphasized, however, that emotional stress *per se* is not the sole causative agent; it is only one of many trigger mechanisms which may set off an allergic reaction in a predisposed person.

Allergic diathesis is thought to be genetically determined. The distribution of genetic predisposition throughout the population, like that of other biologic phenomena, probably occurs in a "bell-shaped" curve, with persons who have a great predisposition to allergic reaction under the slightest stress at one end of the curve and persons who will probably never have allergic disease at the other. Predisposition cannot be measured; development of clinical allergic disease is the only conclusive evidence of its existence. For example, many persons in whom there is no clinical evidence of allergy have positive reaction to skin tests.[14] It may be postulated that later, under the proper circumstances, allergic disease might develop in them.[1] It has been observed that persons with a family history of frequent, severe allergic disease (strong genetic predisposition) tend to have clinical manifestation of allergy early in life. Apparently a specific sensitivity is not inherited, since the presence of circulating antibodies in newborn infants has never been conclusively demonstrated.[2]

The study of clinical evidence of allergy in identical twins should be of interest, since such twins have identical genetic endowments. There have been few such studies, owing to the difficulty of collecting the necessary clinical data.[4, 17] As a matter of fact, the entire problem of genetic transmission in allergic susceptibility is not well defined.[16] If identical twins have clinical manifestations of allergy which differ in time of onset, severity, and reaction pattern, it may be assumed that, since their genetic pattern is

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identical, other factors must modify the organism's response.

It is probable that emotional stress is one of the many factors which modify the organism's response and cause the differences between clinical manifestations in identical twins.

The authors have had opportunity to study a pair of young male twins, A and B, who fulfill the inferential criteria of identity. Unfortunately, complete proof is lacking; the twins were born at home and the placenta was not examined at the time of birth.

A and B are 26 years of age. A has had perennial allergic rhinitis since early childhood and intermittent bronchial asthma since the age of 17 years. B has had sporadic allergic rhinitis since the age of 9 years and intermittent bronchial asthma since he was 24 years old.

The following members of the family are known to have had asthma: Paternal grandmother and her family, maternal aunt, maternal grandfather, and the two-year-old daughter of B. The three-year-old son of A has mild atopic eczema.

A had a short episode of "croup" at the age of 6 years; B had one episode of hives at the age of 5 or 6 years and "chest trouble" for several months at the age of 9 years. A has had perennial allergic rhinitis since early childhood; in B's case, allergic rhinitis began later and has not been as frequent or severe. A had edema and itching of the eyes, following a first and only injection of penicillin when he was 21 years old. A has also had several episodes of conjunctivitis since the age of 21 years. A had edema of the lips after eating crab at the age of 25 years. Subsequently, he ate crab, but had no allergic reactions. B had conjunctivitis, which was diagnosed as chronic non-specific keratoconjunctivitis and which responded to local application of cortisone, when he was 26 years old. Both twins have had frequent canker sores since childhood.

On physical examination, A was found to be slightly heavier than B. The nasal mucosa of both twins was slightly edematous and pale, and a thin watery discharge was apparent. Upon examination of the lungs of both patients, musical rhonchi and expiratory wheezing were heard. Early emphysematous changes were noted in A.

Numerous eosinophils were observed in stained specimens of nasal and bronchial secretions from each twin.

Both A and B had strong positive reactions to scratch tests with house dust. Neither had reactions to either scratch or intradermal tests with other miscellaneous inhalants, and there was no reaction to scratch tests with various pollens of trees, grasses and weeds. A had positive reactions to scratch tests with fresh frozen crab and shrimp, as well as to extracts of crab and shrimp, but results of all other scratch and intradermal tests with foods were negative. B had positive reactions to scratch tests with fresh frozen chicken, anchovy, cod, and sole; but he did not have reactions to scratch and intradermal tests with extracts of these and other foods.

Factors indicating the subjects were identical twins were:

1. The blood groups were identical: O, Rh_0, Rh_1, Rh″, Hr′, Hr″, and MN positive.

2. Great similarity in bony structure, including dentition, as determined by x-ray examination.

3. Somatotyping performed by an independent observer strongly supported true identity.

4. Fingerprints were compatible with identity.

Both parents and one older sister, aged 37 years, are living. The father has had myocardial infarction and has occlusive vascular disease. The sister has diabetes.

The father is a successful businessman, active and extroverted, who drinks and smokes heavily. He was described by the twins as a "good guy, but with little time for the family." The mother has a rather dominant personality, is of rigid demeanor, has a strict religious and moral code, is demanding of husband and children, stressing obedience, and has a great desire to achieve social and financial standing. Despite long-standing marital discord, there has been no formal separation, since both parents are satisfied to go their separate ways. The twins respect and admire their sister, although because of the difference in ages their relationship with her is not close.

A is 15 minutes older than B, and both twins have always felt A was the parents' favorite. A admires and respects his father, wants to please and emulate him but has been somewhat passive in their relationships. The father treats A as though he were still a young boy. Although A respects his mother he has never felt the same affection toward her that he feels toward his father.

B apparently likes his father, but is no more than tolerant of what he regards as his father's weaknesses (for example, "little time for the family"). It is B's opinion that his parents' success is owing to the mother's domination, perseverance and drive. He also said that his mother is the stronger person. As a child, although he resented her demands and his need to comply with her wishes, he felt closer to her than to his father. He finds difficulty, however, in verbally expressing any feeling of true affection for her. It appears that B has always felt rejected by both parents and has reacted with hostility and strong efforts to gain independence. He feels that his mother made more demands on him than on A and that A in some way could "get around" her.

As children, the twins were both aware of their

rivalry. A was always a little larger physically and more popular in school, but B was the better athlete and a better student. A believes he had more natural athletic ability but did not try as hard as B did. During their senior year in high school when they were 17 years old, A had his first attack of asthma, which lasted three months. At the time he was temporarily away from home and working part-time.

After finishing high school, the twins joined different branches of the armed services. A had no attacks of asthma (allergic rhinitis?) while in the service and felt he was successful in his service career. Apparently he liked the idea of separation from his parents. While A was in the service, he married a girl two years older than he. The marriage has been happy. The couple has two sons, 6 and 3 years old. The youngest has very mild atopic eczema.

B did not like the service and was rather unhappy, but had good health. Soon after he was discharged, B married a girl three years younger than he. They have three daughters, aged 4, 2, and 1 year. The two-year-old daughter has had several attacks of wheezing respiration. B's wife is not of his religious faith, which apparently was and is disturbing to his mother. B and his wife disagree about religion and the religious education of the children. In religion, as in other areas, B has a rather intellectualized approach and has "his own concepts of religion." Apparently B does not like his wife's parents and prefers to have little contact with them. In spite of these problems, the marriage seems stable.

After being discharged from the service at the age of 20 years, A returned to school and was free of asthma until a severe attack developed the week before final examinations and persisted until a week after examinations. He began professional school one year later, and again asthmatic attacks occurred before and continued through examinations. He withdrew from school for one year because of asthma and conjunctivitis. During that year, he was free of asthma, although he lived in the same home. Upon resuming schooling, he had asthma before and during every final examination. Yet he had an admirable academic record. Since he has been practicing his profession, he has had attacks during periods when he was under pressure to "produce and succeed." A believes that tenseness, nervousness, and being under pressure are the major precipitating factors.

B also reentered college after being discharged from the service and at about the time of his marriage. He floundered for two or three years, not knowing what career to pursue. He tended to follow the lead of A in choosing a course of study and finally decided to follow the same profession. At the age of 24 years, he entered professional school and moved to a new locality. One year later, after he had lived in the new locality for eight or more months, he moved to a new home in the same town. Soon afterward he had his first attack of asthma. Subsequently he moved to another house in the same block, but asthmatic attacks persisted. The following summer he worked in an area about 25 miles from his home and returned home every night. During this period he was free of asthma. B's attacks of asthma apparently have never been as severe as A's and are not precipitated by the stress of examinations. B associates attacks with feelings of guilt about not working or studying. He has a need to work hard and is reluctant to accept help from his family.

In summary, A has a great need to succeed in order to please other people. His whole life is directed toward achieving success so that he will be acclaimed by his family and friends. Every move seems to be calculated on the basis of what people will think about him. It may be that he is continually striving to maintain his favored position in reference to his twin brother. In any event, his overt personality is such that he is socially acceptable; he is pleasant, ingratiating, and makes an effort to have people like him. It is obvious, however, that when he is faced with a situation in which he must prove his ability to others — in tests, for example — the tension is so great that it precipitates an attack of asthma.

On the other hand, B seems to have a different attitude. It appears that he responded to A's favored position and his mother's demands by reacting with open hostility and denial of dependence. However, there is some identification with the mother, in that he is compulsive and rigid in his beliefs. In adult life he has tended to intellectualize all his problems and to distrust emotions. Once he is certain of the correctness of his ideas, he is willing to argue with anyone. He may even go out of his way to provoke an intellectual debate, thus providing a release for hostility. He is conscious of his rivalry with A and is continually trying to outdo him. Because of his somewhat rigid and combative exterior, he is not as socially acceptable as A and, it seems probable, not as well liked. Since his asthma was later in onset and not as severe, however, it may be assumed that he is more effective in handling his inner tensions.

Thorough psychological testing of the twins has been carried out by an independent observer. It is of interest that their intelligence quotient scores were very close. In general, the psychologist's impression coincided with the clinical formulation.

Because of the family history, it is assumed that these twins have a strong genetic allergic diathesis. Consequently their tissues respond to certain stimuli by the development of edema, hypersecretion, and smooth muscle spasm—that is, clinical allergic disease. The twins were demonstrated to have immuno-

logic allergy—the capacity to react to certain agents —as well as clinical allergic disease. However, it is known that clinical allergic disease may occur in the absence of demonstrable immunologic allergy—that is, factors other than antigen-antibody reactions may produce the pathophysiologic response defined as clinical allergic disease.[8-12, 13, 19] It has been shown that emotional stress may be accompanied by vascular changes that are identical with those seen in immunologic allergy.[8-12, 19] These vascular changes, namely, decreased constrictor tone of arterioles and capillaries, accompanied by increased permeability, are thought to be due to the liberation of acetylcholine at vasomotor nerve endings. Holmes[10] demonstrated that such vascular phenomena can be produced in the nose, following interruption of sympathetic vasoconstrictor nerves by injection of procaine into the stellate ganglion.

It is probable that both immunologic allergy and non-allergic vascular phenomena are of importance in producing clinical allergic reactions in a given person. At one time the immunologic phase may predominate, while at another time non-allergic vascular reactions may be of primary importance. Holmes[10] reported that the severity of clinical allergic response following exposure to an antigen may be greatly modified by the preexisting vascular status of the tissues involved. This may be the physiologic explanation for the clinical observation that a given subject may have clinical allergic response on exposure to a known antigen under one set of circumstances, and at other times have no clinical response to the same antigen. The thesis that changes in autonomic innervation may modify allergic phenomena is supported by the observation of Funkenstein[6] that variations in an individual's physiologic responses to injected acetylcholine and epinephrine are related to activity or remission of clinical allergic disease.

The twins reported upon here, in whom the genetic background is identical, are strikingly different with regard to allergic manifestations. The age at onset was not the same and there was no similarity in the pattern of attacks. Both were demonstrated by immunologic means to be sensitive to house dust and certain foods. There was no clinical evidence to suggest that food was an important antigenic agent in the development of rhinitis and asthma in these patients. It can be assumed, however, that exposure to house dust was important. The exposure of the twins to house dust was relatively constant, although the clinical manifestation of allergy, especially in the case of A, usually occurred in connection with particular types of stress. The authors believe that emotional stress is accompanied by certain physiologic changes which precipitate clinical allergic disease, and that in the twins herein reported upon both immunologic allergy and the pathophysiologic vascular changes accompanying emotional stress are of importance in the genesis of clinical allergic reactions.

The differences in the types of situation that produce emotional stress in these twins may be understood in the light of their personality development. The overt stress-producing situations are more clearly defined in A than in B and can be more clearly correlated with the development of episodes of clinical allergic disease. It is of interest that although A is on the surface a better adjusted individual, the price of this adjustment is more frequent emotional tension which is reflected by an increased incidence of clinical allergic manifestation.

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Surgical Treatment of Infantile Hydrocephalus

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• The operation of endoscopic coagulation of the choroid plexuses for the relief of infantile hydrocephalus is now 18 years old. Nearly a hundred cases have been reported and the indications and procedure are well standardized. Several patients have grown up apparently normally from the earliest series of operations.

In a recent series of 20 operations performed on ten patients in the past ten years, there have been no deaths attributable to the procedure. The operation has substantially decreased the pressure in all cases, and has brought it within normal limits in all cases in which it was performed before the head became grossly enlarged.

The mentality has improved following relief of pressure in all cases. When the operation was performed before deterioration began, the results were uniformly excellent.

THE CONDITION of infantile hydrocephalus is unmistakably portrayed in ancient Greek votive statuettes, but the first written description of it apparently was that of Celsus.[1] He described a disorder of infants "where the fluid distends the skin, causes a swelling of it, and yields to the pressure of the finger: This the Greeks call hydrocephalus."

This early description calls attention at once to the fundamental characteristic of infantile hydrocephalus—the increase of intracranial pressure. The remaining clinical details were gradually filled in during the 19th century; namely, that hydrocephalus is a common disorder, occasionally present at birth but more likely to come on during the first year of life; that it is often associated with spina bifida, and may be precipitated by the repair of a meningocele; and that children afflicted with the condition sometimes survive to adult life, occasionally with intelligence unimpaired. Unfortunately, a serious error was introduced by the pathologic anatomists of that period—confusion between the condition of increased intraventricular pressure or true hydrocephalus according to Celsus, and the enlargement of the cerebral ventricles resulting from atrophy, formerly called "hydrocephalus ex vacuo."

The distinction between spontaneous infantile hydrocephalus and tuberculous meningitis became clear with the introduction of lumbar puncture. Recognition of the physiologic features of the condition resulted from the work of Dandy and Blackfan in 1918 and laid the foundation for a sound surgical approach. Gradually during the following two decades the condition of subdural hygroma became familiar to pediatricians, and the surgical treatment became established. Cases of hydrocephalus resulting from obstruction of the aqueduct by tumors, atresia or inflammatory diseases (such as toxoplasmosis) have been reported from time to time.

This presentation deals solely with the treatment of spontaneous communicating infantile hydrocephalus, with or without meningocele. Medical treatment of this condition appears now to be abandoned and spontaneous recovery is so rare as to elude statistical evaluation. A variety of surgical procedures are now available, however. One of them, to be described in detail, has been well standardized for 18 years and can now be performed with little hazard and with a high proportion of excellent results in well selected cases.

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DESTRUCTION OF THE CHOROID PLEXUSES

The conception that the spinal fluid is secreted by the choroid plexus originated with Magendie, and isolated attempts (on the whole unsuccessful) to relieve hydrocephalus by destruction of the plexus were carried out in the early years of this century. The possibilities of surgical treatment were, however, first systematically explored by Dandy between 1918 and 1922.[2, 3] He showed experimentally that removal of the plexus caused collapse of a blocked lateral ventricle in animals, and described a technique for removal of the plexus under direct observation in cases of non-obstructive hydrocephalus.[2] He did not present statistical studies of his cases. In 1932[4] he stated that "the survival period has not been long enough to be certain of cures," and in 1938[5] "I have had several undoubted cures resulting from this method."

The author's technique was published in 1934.[6] It is based on the use of a distinctive type of coagulating endoscope with a rod of optical glass serving as a viewing system and also as a carrier for two electrodes and a lamp. The instrument gives several

Figure 1.—*Left*, photograph of patient in third month of life just before coagulation of choroid plexuses. *Center*, patient at six years of age. *Right*, at time of graduation from high school.

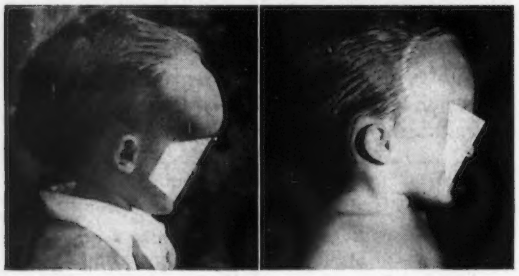

Figure 2.—*Left*, patient at three years of age just before endoscopic coagulation of the choroid plexuses. *Right*, two and one-half years later, after reduction of intracranial pressure had permitted plastic repair of elevated flap of transfrontal operation performed elsewhere. Intracranial pressure was normal at last report.

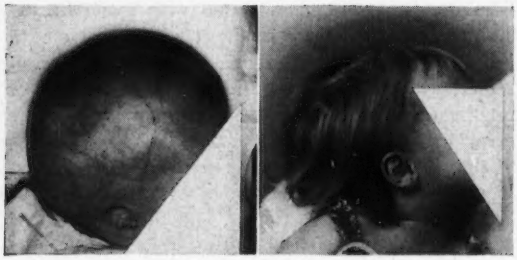

Figure 3.—*Left*, patient at five months of age just before coagulation of choroid plexus. *Right*, patient a little more than two years later. At time of last report, intracranial pressure was normal.

advantages. First, it provides an extremely wide optical aperture, which permits visualization of the ventricular contents even when the fluid is bloody. Second, no current passes through the brain; there is a small intense electrical field between the electrodes. Third, the diameter of the instrument may be kept sufficiently small to permit introducing it into the frontal and temporal horns even before the ventricles have become greatly dilated. This instrument was developed after unsuccessful trial of conventional endoscopes bearing unipolar coagulating electrodes. The employment of these tended to produce necrosis of the floor of the ventricle, and the operative field was poorly seen. An endoscope of the conventional type, with provision for irrigation, was devised by Scarff in 1936[8] and he still employs it, with excellent results.[9, 10] In the most recent series of 19 cases reported upon by Scarff there was only one "operative" death, and the result was excellent in 15 cases. Other surgeons have reverted to Dandy's method, but no significant statistics are reported.

RESULTS

The author's results were last fully reported in 1943.[7] Disregarding other conditions, 71 operations were reported on 42 patients, with 11 operative deaths, of which seven occurred in the first 17 cases. Since then, 20 operations of this type have been performed, upon ten patients, with no operative deaths.

It has not been possible to get continuing follow-up reports on three of the patients, who were operated upon in New York between 1943 and 1946, but all were doing well in 1946. Of the seven patients operated upon since 1947, four are still alive and doing well, with maintenance or improvement of mentality. One patient who was incompletely re-

lieved by cauterization of the choroid plexuses and then by an additional ventriculomastoidostomy, has done well since a tube was inserted from the subarachnoid space into the peritoneal cavity. One was apparently relieved of hydrocephalus but died of unrelated causes. One died following an attempt at third ventriculostomy.

Since many detailed case reports have been presented by Scarff[9, 10] and by the author in previous publications, only a few general observations on the indications for operation, on details of technique and on results need be set down here.

First, this operation is a safe one—safer perhaps than ventriculography in such cases, and apparently safer than the recently proposed drainage operations. In the early stages of the disease it is probably safer to operate than to wait in the hope that it will become arrested spontaneously.

Second, the outlook is excellent if patients are referred for operation before the mentality is affected and before there is irreparable damage to the brain. Ideally, the decision for operation should be made when the presenting symptom is a swelling of the fontanelles and infantile hydrocephalus has been diagnosed on the basis of a ventricular puncture with the patient under sedation—a procedure which serves to rule out meningitis, toxoplasmosis, and subdural hygroma and usually renders ventriculography unnecessary.

Third, prognosis depends chiefly upon the patient's intellectual endowment at the time of operation, but the degree of enlargement of the head and thinning of the cortex are limiting factors. Sometimes a patient with enormous ventricular dilation may have an unexpected degree of intelligence and Scarff[9] has shown that the ventricular wall may grow thicker following relief of intracranial pressure. Gross enlargement of the head may produce secondary adhesions about the base, in which case destruction of the plexuses may not completely relieve the pressure. Many of the poor results, both in the author's series and in Scarff's, would undoubtedly have been avoided had the patients been operated upon sooner.

Fourth, operation may be considered justified even when the patient has mediocre mentality and gross enlargement of the head. Such persons do not necessarily die; they sometimes grow up to adult life with monstrous heads and progressively impaired mentality. It may seem wiser to attempt to arrest the accumulation of fluid and preserve the remaining mentality. Despite relief of pressure, however, patients with poor mentality appear to have a poor life expectancy.

Fifth, ventriculostomy of various types may prove helpful as an adjuvant to cauterization of the plexus, which appears to be the operation of choice in cases of communicating hydrocephalus. Certainly the drainage operations are more likely to succeed and less likely to lead to complications if the production of fluid is restricted.

Sixth, certain technical refinements have been added to the technique published by the author in 1943.[7] Suture of the pia to the dura minimizes the danger of collapse of the ventricle at operation, or the formation of subdural cysts. Suture of the periosteum over the suture line decreases the danger of leakage. Drainage of the ventricle through a tiny plastic tube diminishes the postoperative reaction (and in one case this device made it possible to operate on both sides at one time).

Seventh, always after cauterization of both sides, reinspection should be carried out to make quite certain that no tags of plexus were left behind. This is particularly important if the preliminary operations were performed with a ventriculoscope of the cystoscope type.

Eighth, coagulation of the plexuses may be of great help in the treatment of other conditions involving increase of intracranial pressure—for example, postmeningitic hydrocephalus, and large, tense, sessile meningoceles which do not destroy the function of the sphincters.

DISCUSSION

Infantile hydrocephalus is a common condition, perhaps as common as harelip or clubfoot. The condition is easy to recognize, even in early stages. There is a well established surgical operation which entails little hazard and offers an excellent prospect of relief in early cases. To permit one of the unfortunate children with promising mentality to slip past the period of election without a trial of operation is no more conscionable than to permit a patient with meningitis to go without antibiotic drugs.

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ADDENDUM

After this communication was written, a brief review of a presentation of the surgical treatment of hydrocephalus by Walker* became available. It is summarized in the following quotation:

On the basis of the medical literature and the records of the Johns Hopkins Hospital, the results at the end of two years were as shown in the tabulation:

Operation	No. of Cases	Operative Mortality	Results After Two Yr.† Alive	Dead
Plexotomy	194	70	31	105
Third ventriculostomy	197	44	39	81
Arachnoido-peritoneostomy‡	105	12	41	6
Arachnoido-ureterostomy	86	6	17	28
Ventriculo-cisternostomy	25	8	9	9

† Only the patients whose states were definitely known two years after operation coded.

‡ Based largely on the series of Arendt whose results are not well documented.

It is not clear whether "plexotomy" includes endoscopic coagulation, or whether it refers to Dandy's operation of removal of the plexus. In either case, a comparison between this table and the results reported in the present article speaks for itself.

* Walker, A. E.: A Critique of Surgery for Hydrocephalus (abstract of society presentation), Archives of Neurology and Psychiatry, 67:822-823, June 1952.

New Film Catalog

A REVISED LIST of medical and health films has been prepared by the A.M.A.'s Committee on Medical Motion Pictures. Brief descriptions, running time, and rules and regulations are included in the catalog for 78 medical films which are available from the committee. Copies of the list may be obtained from the committee.—*From A.M.A. News Notes.*

Hearing Impairment in Children

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• Abnormal behavior in children may frequently be caused by impairment of hearing. Early detection of the impairment and of the cause are of utmost importance, not only to prevent irreversible changes where that is possible, but to permit early beginning of special training for children who are permanently deaf.

Recent studies have shown that deafness of infants may follow rubella in the mother in early pregnancy, or kernicterus caused by Rh incompatibilities. Measures to control these disorders are being investigated. Adequate and careful treatment of diseases of the nose, as well as surgical drainage of infected ears when necessary, are important factors in the prevention of hearing loss in children.

GREAT STRIDES have been made in recent years in the treatment and rehabilitation of persons who are hard of hearing. Excellent results in the alleviation of deafness due to otosclerosis with refinements in the technique of the fenestration operation have been a needed stimulus, as has been the equally optimistic prognosis in overcoming the handicap of deafness in the aural rehabilitation centers of the armed forces. Prevention of deafness is the stressed aspiration in present-day otology.

The study and treatment of children with conditions resulting in lessened acuity of hearing are the means available to greatly diminish the number of hard-of-hearing persons. The more common of these conditions is the basis of this discussion.

It has been estimated by Silverman[11] that there are approximately 1,500,000 hard-of-hearing school children in the United States and 18,000 deaf children of school age. Classification into these two distinct groups is, of course, arbitrary, depending upon the degree of hearing impairment. A deaf child is defined as one in whom there is insufficient residual hearing to enable him to make use of hearing for ordinary communication. A hard-of-hearing child is one whose hearing is less than normal but who has sufficient residual hearing for communication either with or without a hearing aid.

The estimate of the number of deaf children is probably accurate, for these children are undertaking definite educational programs either in special classes in local school systems or in one of the numerous schools for the deaf. Accuracy of the estimate of number of hard-of-hearing children is questionable, since no definite criteria have been established universally and the degree of loss of acuity necessary for reporting varies in different parts of the country.

The magnitude of the problem of hearing impairment is indicated by the estimates with regard to children of school age. In addition there are thousands of children of preschool age with hearing loss—in many cases undetected during a period when treatment should be under way. Too many children are classified as backward, dull, maladjusted misfits, when in reality their difficulty is attributable to hearing impairment which can be alleviated or, if irreversible, overcome as a handicap to normal living in society.

Much of the solution of the problem lies in early diagnosis, which depends in large measure upon careful observation of children by physicians in general practice. Not only can a family physician make a diagnosis and begin treatment early, but by observing and recording the child's early history as well as family history he can add immensely to knowledge of the causes of hearing impairment. It was observations of this kind that gave first clues to the part played by rubella in causing deafness in infants.

CONGENITAL DEAFNESS

Congenital deafness in 30 to 35 per cent of cases is thought to be of Mendelian hereditary type (Kinne).[8] Anatomical malformations, syphilis during pregnancy, other severe infectious diseases, and the ingestion of toxic agents, including quinine early in pregnancy, are known causes of congenital deafness.

The dangers of syphilis during pregnancy have been greatly diminished by current policies of prenatal serologic studies. In recent years chemotherapeutic agents have controlled the severe infectious diseases thought to cause congenital deafness when they occur during pregnancy. Use of toxic agents in

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attempted abortion may have been reduced by the knowledge that they may cause deformities in the infant if abortion is not accomplished.

In recent studies two important etiological factors have been noted—maternal rubella and Rh factor incompatibility.

During the years 1940 to 1942 there was a widespread rubella epidemic in Australia and a large number of pregnant women had the disease. Later it was noted that among the progeny of women who had rubella during pregnancy the incidence of congenital defects was exceptionally high. Congenital cataracts, patent ductus arteriosus and perception deafness were the most common defects. These abnormalities were found to be most prevalent in children whose mothers had had rubella in the first trimester of pregnancy. Carruthers,[1] reviewing the combined reports of several Australian investigators, noted 74 cases of perception deafness in the offspring of 102 women known to have had rubella during the first three months of pregnancy. Goodhill,[5, 6] in a survey in this country of 904 cases of profoundly deafened children, found maternal rubella to be the most probable etiological factor in 20.5 per cent of them. Other studies have concurred and definitely established that deafness is a common sequel of maternal rubella if the infection is early in pregnancy.

The deafness is probably caused by the hindrance in the normal development of the primitive cells forming the organ of Corti. This development takes place during the first three months of fetal life. In studies of temporal bones of two fetuses by Schall[10] and of one infant by Carruthers, maldevelopment and blood vessel changes which probably brought on cochlear deficiencies were noted. In each instance the mother had rubella during the first four months of gestation.

Prevention of rubella during early pregnancy is of utmost importance. Isolation, although desirable, is impractical. It has been proposed that, until methods of immunization are found, young girls be exposed intentionally, lest they later contract the disease when pregnant.

Kernicterus sometimes is closely associated with severe degenerative defects in infants. In 1949 Goodhill,[5, 6] reporting on the relationship between the Rh factor and perception deafness in children, noted that there was history of erythroblastosis fetalis in an inordinate proportion of cases. The coincidence was noted in Rh-positive children of Rh-negative mothers who had been sensitized by previous pregnancies.

Crabtree and Gerrard[2] reported 16 cases of perception deafness in children who had had severe neonatal jaundice. In 14 cases the jaundice resulted from iso-immunization. There was no relationship between the degree of deafness and the extent of extrapyramidal lesion. Of 27 perception-deaf children who Goodhill believed had probably had erythroblastosis fetalis, nine were spastic.

Deafness in cases of this kind probably is due to the toxic effect of kernicterus on cranial nuclei. Bile staining in the cochlear nuclei has been noted at postmortem examination. It may be that such damage takes place in subclinical erythroblastotic jaundice also. Further careful investigations must be carried out before it will be possible to determine how often erythroblastosis is associated with perception deafness.

There is no known means of preventing deafness in children of sensitized Rh-negative women. What effect, if any, treatment of erythroblastotic infants as outlined by Dennis[3] will have on the incidence of deafness cannot be determined until more data are available.

Not hearing speech, a child born deaf is mute also until he can be taught speech patterns by special means. No medical or surgical treatment for the alleviation of congenital deafness has been found, but great strides have been made in special schools, public and private, in providing means for congenitally deaf children to overcome the handicap. The diagnosis of deafness must be made early and it is the responsibility of physicians undertaking the general care of children to be on the lookout for this defect and to advise parents.

ACQUIRED PERCEPTION DEAFNESS

Perception deafness may be caused by injury to the head, at birth or later, or by severe infectious diseases, such as scarlet fever, measles, influenza, mumps and, especially, meningitis, which is thought to be the cause in 7 to 10 per cent of all cases of acquired perception deafness. Since the advent of streptomycin and, with it, improved prognosis for patients with tuberculous meningitis, question has arisen as to whether deafness is caused by the drug or the disease. The present consensus is that long continued use of streptomycin or dihydrostreptomycin will cause damage to the vestibular and auditory mechanism. Glorig[4] reported that dihydrostreptomycin may cause irreversible perception deafness, whereas the effect of streptomycin is most pronounced on the vestibular apparatus. Streptomycin, therefore, would seem to be the drug of choice if long term therapy is indicated, assuming that disturbance of balance is a lesser handicap than perception deafness.

Prevention of acquired perception deafness in children calls for avoidance of trauma at delivery.

General immunization, including the use of immune globulin in measles, and the availability of antimicrobial agents have reduced the incidence and the severity of the infectious diseases previously mentioned as etiologic factors.

HEARING LOSS OF CONDUCTION TYPE

Hearing loss of conduction type is much more common in children than is perception deafness. It is caused by abnormalities in the external auditory canal, in the tympanic membrane, or in the middle ear that impair the transmission of sound to the inner ear. Anomalies of the external canal, foreign bodies, impacted cerumen, trauma, and atresia secondary to otitis externa are not uncommon etiologic factors. Distortion of the tympanic membrane, infection of the middle ear, poor aeration of the middle ear, and disease of the ossicular chain and stapedial foot plate also may cause hearing loss of conduction type.

Infection of the middle ear and impairment of aeration of the middle ear by disease of the eustachian tube are the most common causes of conduction loss in children; and these conditions, if not adequately treated, may result in permanent impairment in adulthood.

Acute purulent otitis media, an acute infectious disease characterized by fever, otalgia, and the development of a purulent exudate in the middle ear, may result in distortion of the tympanic membrane. Antimicrobial agents now available give better control of acute infectious diseases. As Rutherford[9] stated, however, the use of these agents alone in purulent otitis media does not return the middle ear and tympanic membrane to a normal state. Incision of the tympanic membrane for adequate drainage of the purulent exudate from the middle ear is still the treatment of choice either with or without the adjunct of the chemotherapeutic agent specific for the causative organism. When there is spontaneous perforation of the tympanic membrane, it usually occurs in the anterior inferior quadrant and drainage is inadequate and healing poor. Therefore, even in the presence of spontaneous perforation, the prime surgical principle of incision and drainage by careful myringotomy in the posterior quadrant of the tympanic membrane should be applied.

Without myringotomy adhesive processes, middle ear scarring, tympanic membrane distortion, and impaired function with subsequent hearing loss of conduction type may result. A further procedure that should be carried out to preserve normal function of the middle ear after acute infection is inflation of the eustachian tube after the acute disease has subsided and the myringotomy site healed. In children it is good practice to inflate the eustachian tubes before final dismissal following otitis media. The Politzer method is easy and efficient.

Otitis media with effusion—also termed serous otitis media, catarrhal otitis media, or non-purulent otitis media—is an often overlooked disorder characterized by a sterile effusion of thin yellow transudate or thick mucoid exudate in the middle ear. The effusion is brought about by impaired aeration of the middle ear following eustachian tube blockage. It causes pronounced impairment of hearing and, if not treated, results in permanent changes in the middle ear and the tympanic membrane, with irreversible loss of hearing.

Eustachian tube blockage in children is caused by acute nasopharyngeal infection or any condition, mechanical or infectious, which may cause nasal obstruction. Allergic rhinitis, sinusitis and adenoid hypertrophy are the most common causes.

The diagnosis of otitis media with effusion is not difficult in adults, for they complain of discomfort in the ear and of the "head in a rain barrel" sensation. Children, however, are often unaware of the disorder and careful questioning may be necessary to elicit complaints referable to the ears. Parents or teachers, alerted by a child's inattentiveness or irritability or by his tugging at or scratching the ears, may be the first to note definite impairment of hearing.

Usually upon examination the tympanic membrane is observed to be retracted, the short process of the malleus prominent, and the handle of the malleus shortened. A yellow or amber sheen with increased luster of the drum is typical, and unless the entire middle ear is filled with effusion a meniscus of the fluid level may be seen. Applying suction to the external auditory canal with a Siegle speculum is useful in making the diagnosis, as the motion of the fluid or bubbles in the middle ear can then be observed. Hoople[7] and others advocate diagnostic myringotomy in questionable cases.

Treatment is directed at restoration of middle ear aeration. Obviously the underlying disorder causing eustachian tube blockage must be corrected. The eustachian tube must be inflated and if fluid persists it must be removed either by aspiration through a tympanic membrane puncture with a No. 20 short-beveled needle or by myringotomy followed by suction and tubal inflation. In persistent cases repeated myringotomy may be necessary.

In any case in which eustachian tube blockage by adenoid hypertrophy has caused middle ear disease and potential hearing impairment, adenoidectomy should be carried out. The age of the patient is not an important factor. Adenoidectomy should be performed when necessary, not when a child reaches a given age indiscriminately picked as the "age for adenotonsillectomy."

Careful removal of all adenoid tissue is important. Quick thrusts into the nasopharynx with dull curette or adenotome are not to be condoned. Careful palpation of the nasopharynx with the finger or direct inspection of the area by use of a palate retractor, such as a Love retractor, is necessary to insure complete removal. It must be noted that palate retractors for direct nasopharyngeal inspection are of little value unless a mouth gag, separate from the tongue blade, is used. Gags of the Davis type put so much tension upon the tonsillar pillars that the palate retractor cannot be used effectively with them.

Postoperative irradiation of nasopharyngeal lymphoid tissue with either external radiation or radium applicators is a well established procedure although results are not as good as initial studies indicated they might be. Radiation therapy does not take the place of adenoidectomy nor should adenoidectomy be done with less care in anticipation of postoperative radiation therapy.

Radiation therapy is indicated if there is a history of recurrent eustachian tube blockage and nasopharyngeal lymphoid tissue is observed in examination either with a mirror or with an electrically illuminated nasopharyngoscope. Rarely is it indicated before surgical removal of the adenoid tissue.

There is a close relationship between allergic rhinitis and adenoid hypertrophy. Enormous growth of adenoid tissue is common in children with persistent nasal allergic disease, and regrowth shortly after adenoidectomy is frequent. In such circumstances the allergic manifestations must be controlled to restore middle ear function, as operation alone will not suffice.

Restoration of middle ear aeration and reestablishment of normal function of the eustachian tube are the basic factors in prevention of conduction type deafness in children.

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Screening Tests for Diabetes Detection

Combined with a Chest X-ray Survey

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• A program was carried out to test the value and feasibility of performing blood sugar screening tests in conjunction with a community-wide chest x-ray survey. A simple, rapid and inexpensive blood sugar screening test requiring only about two drops of blood from the finger tip was used. Among 14,681 persons who stated that they did not have diabetes, 191 or 1.3 per cent had "positive" results in screening tests. The number of persons referred to their physicians for diagnostic study because of the possibility of diabetes was reduced from 191 to 127 by means of a more specific secondary screening test.

Diagnostic information with regard to 102 of the 127 persons referred to their physicians was supplied by the physicians. In 58 (0.40 per cent of the 14,681 participants) the diagnosis was diabetes—newly discovered as a result of referral by the survey.

Some of the persons referred to their physicians because of suspicion of diabetes, while not then diabetic, might be considered prediabetic. The appearance of diabetes in this group during the year following the survey was therefore investigated. Glucose tolerance tests were performed for 32 of the diabetes suspects whose diagnosis immediately following the survey was either "not diabetic" or unknown. In 15 cases the glucose tolerance curves were indicative of diabetes, in seven cases questionable and in ten cases normal.

The 58 persons diagnosed immediately after the survey plus the 15 found to have "diabetic" glucose tolerance curves a year later made a total of 73 newly discovered diabetics. This is a discovery rate of 0.50 per cent among the 14,681 participants in the survey.

The success of this combined diabetes detection and chest x-ray survey suggests that other screening procedures should be studied to determine the desirability of adding them to similar community-wide case-finding programs.

LABORATORY ANIMALS with experimentally induced diabetes have recovered as a result of early treatment.[11, 12] Recovery did not occur when treatment was delayed for more than three months. Untreated control animals died of diabetes. Cure of spontaneous diabetes mellitus in man has not been proven but there is ample evidence that early treatment improves prognosis.[2, 13, 19] Because of this, the American Diabetes Association has launched a nationwide diabetes detection drive, highlighted each year during Diabetes Week. Over 650 county and state medical societies and many other agencies have actively participated in diabetes detection work.[6] The subject of this report is the pilot diabetes detection project of the Contra Costa Chest X-Ray Survey, conducted in 1951.

Case-finding programs consisting of more than one screening test have come to be known as multiphasic or multiple screening programs. It is obviously more economical to perform several screening tests at one time than to conduct separate programs, each consisting of a single screening test. Also, a multiphasic approach gives better service to persons screened.[3, 4] The practicability of chest x-ray surveys and of diabetes detection projects has been demonstrated on numerous occasions. At least two programs consisting of chest x-rays and determinations of the sugar content of the blood have been reported.[17, 21] The unique feature in Contra Costa County was the combination of diabetes detection with a community-wide rapid tempo mass chest x-ray survey. The objective was to test the value and feasibility of such a combined disease detection program.

The organization and chest x-ray program of the Contra Costa Chest X-Ray Survey have already been reported.[18] The Contra Costa County Medical Society endorsed the program and several of its members served as a medical committee which formulated medical policies for the entire survey. Some of the local physicians were interested in starting a

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diabetes detection program. On being asked to participate in a projected chest x-ray survey at about the same time, they had the idea of combining the two projects. A diabetes subcommittee determined procedures for the diabetes detection program. The Contra Costa Chest X-Ray Survey Corporation conducted the survey. The California State Department of Public Health, Contra Costa County Health Department, City of Richmond Health Department, Contra Costa Public Health Association (county tuberculosis association) and the U. S. Public Health Service assisted in both planning and operational phases.

METHOD

The Wilkerson-Heftmann screening test[23] to determine whether the sugar content in the blood is above or below a certain level was selected as the one most suitable for the project. It requires only about two drops (0.1 ml.) of blood, which is easily obtained from the finger tip. With the aid of a machine called the Hewson Clinitron, tests can be performed at a maximum rate of 120 per hour. The test indicates whether sugar content in the blood is above or below a selected screening level. The Wilkerson-Heftmann screening test is a "true blood sugar" method—that is, it does not reflect significant amounts of non-glucose reducing substances. This is in sharp contrast to the more familiar Folin-Wu test, which includes non-glucose reducing substances to a considerable and variable extent.[8, 10, 14, 15] Because tests of the blood for sugar are more sensitive and more specific for diabetes than urinary sugar tests,[7] urine specimens were not obtained. Only capillary blood was used in this program, although the Wilkerson-Heftmann method may be also used for venous blood. In the fasting state capillary and venous blood sugar values are almost identical. Following a carbohydrate meal, the sugar content of capillary blood rises higher and remains somewhat higher than does that of venous blood for at least three hours.[14]

An intensive publicity campaign urged the public to participate in the chest x-ray survey. Eighteen minifilm x-ray units were operated for varying periods in many locations throughout the county. Two to four of the 18 x-ray units were staffed with additional clerks and laboratory technicians for registration and collection of blood specimens. Because blood sugar screening tests were available at only a few of the x-ray units, no community-wide publicity was given to this phase of the program. The tests were simply offered as an additional service to persons who came to certain locations for a chest x-ray.

All participants were asked, "Do you have diabetes?" and, "Did you eat or drink anything during the last two hours?" For persons who answered "No" to the second question or who had consumed only non-caloric fluids, the dividing line selected for screening was 130 mg. of sugar per 100 cc. of blood. For others the dividing line was 180 mg. per 100 cc. All participants were notified of their test results.

Primary screening tests are not diagnostic, and appropriate medical and laboratory examination will show that a certain proportion of persons with "positive" results in screening tests are in good health. Secondary screening tests, while still not diagnostic, are more specific. They are designed to save both physicians' and patients' time by minimizing referrals of persons who do not have the disease the tests are designed to detect. Persons who stated they did not have diabetes and whose primary screening test indicated blood sugar content above the screening level were asked to return in a fasting condition to a Retake Center for a secondary screening test. They were given 50 gm. of dextrose orally and one hour later a specimen of capillary blood was obtained and tested to determine whether the sugar content was above or below 180 mg. per 100 cc. These recheck or secondary screening tests were not done with the subject in the fasting state because even persons with diabetes may have normal content of sugar in the blood while fasting.[1, 2, 20] Part of the hour between administration of dextrose and collection of the blood specimen was used for an interview with a public health nurse. The nurse explained that the screening tests are not diagnostic—that they merely select out of a group of persons the few who should visit their physicians at once because of the possibility of diabetes. Questions were answered and further information given to prevent undue anxiety. The nurse also obtained the name of the physician to whom a report should be sent if test results indicated need for further observation. The following criteria for referral to physicians were used: (1) primary screening test showing over 180 mg. of sugar per 100 cc. of blood, regardless of secondary screening test result, or (2) primary screening test showing over 130 mg. per 100 cc. and secondary screening test over 180 mg. per 100 cc. or not accomplished.

Persons who stated they had diabetes and who had had blood sugar content above the screening level were also asked to return for a recheck test. However, they were not requested to report in fasting condition and were not given a test meal. The reasons for asking them to return were to determine whether they had lapsed from regular medical care, to impress upon them the importance of continuing medical supervision, and to obtain names of their physicians.

To evaluate results of the survey, physicians were asked to report whether a diagnosis of diabetes was established and whether the diagnosis, if any, was made as a result of referral by the survey. With regard to persons previously known to have diabetes, physicians were asked whether the patient had been following medical treatment for diabetes with reasonable regularity, and if not, whether the patient made at least one visit as a result of the survey.

Some of the persons who were referred to physicians on suspicion of diabetes, while not diabetic at the time of referral, might be considered "prediabetic." A recently reported study[9] of 55 "prediabetic" persons who were observed for one to 25 years showed that diabetes eventually developed in 33 cases. Accordingly, it was considered worthwhile to reexamine some of the diabetes suspects a year after the survey. This follow-up consisted of a standard three-hour glucose tolerance test. The Folin-Wu method of determining sugar content of the blood was used because it is the one with which physicians in this area are most familiar.

TABLE 1.—*Number of Persons Tested, Number of "Positives" and Per cent of "Positive" by Screening Level*

Screening Level	Number Tested	Number "Positive"	Per cent "Positive"
Not Previously Known Diabetics			
130 mg. per 100 cc.	7,373	141	1.9
180 mg. per 100 cc.	7,308	50	0.7
Total—both levels	14,681	191	1.3
Previously Known Diabetics			
130 mg. per 100 cc.	104	39	37.5
180 mg. per 100 cc.	78	29	37.2
Total—both levels	182	68	37.4

PRIMARY SCREENING TEST RESULTS

One hundred ninety-one (1.3 per cent) of the 14,681 persons screened who said they did not have diabetes had blood sugar values above the stated screening levels. Among the 7,373 screened with 130 mg. of sugar per 100 cc. as the dividing line (because of a negative answer to the question, "Did you eat or drink anything during the last two hours?") 141 or 1.9 per cent had blood sugar content on the "positive" side of the line. Of the 7,308 persons screened at 180 mg. per 100 cc., 50 or 0.7 per cent had "positive" results. The difference between the "positive" percentages in these two groups may be attributed in part to inaccuracy of answers to the question concerning recent ingestion of food.

Of the 182 previously known to have diabetes, 68 (37.4 per cent) had blood sugar values above screening levels. There was no significant difference between the proportion of "positive" results among those screened at 130 mg. per 100 cc. of blood and the proportion among those screened at 180 mg. per 100 cc. The percentage of "positive" results was substantially the same for 61 males as for 121 females. Age proved to be a significant factor. Twenty-four per cent of 79 diabetic persons under age 50 and 48 per cent of 103 who were 50 years of age or older were "positive" in screening tests. Fourteen of the 182 persons previously known to have diabetes stated at the time of the primary screening test that they did not have the disease. When reporting for the secondary screening test, eight of them stated that they had known even at the time of the first test that they had diabetes. Information about existence of previously known diabetes in the other six was obtained from their physicians.

TABLE 2.—*Number of Tests of Persons Not Known To Have Diabetes, Number "Positive" and Per cent "Positive" by Screening Level, Age Group and Sex*

Screening Level	Age Group	Total			Male			Female		
		No. Tested	"Positive" No.	"Positive" Per cent	No. Tested	"Positive" No.	"Positive" Per cent	No. Tested	"Positive" No.	"Positive" Per cent
130 mg. sugar per 100 cc. of blood—	Under 20	377	5	1.3	179	3	1.7	198	2	1.0
	20-29	1,567	8	0.5	686	4	0.6	881	4	0.4
	30-39	1,987	21	1.1	804	8	1.0	1,183	13	1.1
	40-49	1,511	31	2.1	699	17	2.4	812	14	1.7
	50-59	1,067	46	4.3	500	26	5.2	567	20	3.5
	60-69	587	21	3.6	273	9	3.3	314	12	3.8
	70 & over	225	9	4.0	125	6	4.8	100	3	3.0
	Unknown	52	....	....	19	....	....	33	....	....
	All ages	7,373	141	1.9	3,285	73	2.2	4,088	68	1.7
180 mg. per 100 cc.—	Under 20	639	3	0.5	294	1	0.3	345	2	0.6
	20-29	1,754	11	0.6	735	7	1.0	1,019	4	0.4
	30-39	1,996	8	0.4	895	5	0.6	1,101	3	0.3
	40-49	1,414	5	0.4	706	4	0.6	708	1	0.1
	50-59	860	11	1.3	402	5	1.2	458	6	1.3
	60-69	458	11	2.4	259	9	3.5	199	2	1.0
	70 & over	142	1	0.7	76	....	....	66	1	1.5
	Unknown	45	....	....	14	....	....	31	....	....
	All ages	7,308	50	0.7	3,381	31	0.9	3,927	19	0.5

TABLE 3.—*Secondary Screening Test Results of Persons Not Previously Known to Have Diabetes*

Screening Level (mg. of sugar per 100 cc. of blood)	Original Screening Test: Number "Positive"	Secondary Screening Test*: Number Tested	Secondary Screening Test*: Number "Positive"	Secondary Screening Test*: Per cent "Positive"
130 mg.	141	123	59	48
180 mg.	50	41	25	61
Total—both levels	191	164	84	51

* Participants reported in fasting condition. They were tested at the 180 mg. per 100 cc. screening level one hour after ingestion of 50 grams dextrose.

Table 2 gives screening test results for persons who stated they did not have diabetes. In general, the percentage of "positive" results was higher among males than females. The incidence of "positive" was more than three time as great in persons of age 50 and over as it was in younger persons.

The screening tests for blood sugar content proved to be much more popular than it was thought they would be. On many occasions persons who wished to have the test did not get it because there were not enough technicians on duty. This was particularly true of a shopping district location at which 14,986 chest x-rays were taken and only 6,250 specimens of blood were obtained. Lack of space made it impossible to have more than one technician obtaining specimens of blood at this testing station. At four of the 15 locations (exclusive of Retake Centers) where blood sugar tests were available, the number of blood specimens obtained exceeded the number of x-rays taken. In two of these instances the number of blood sugar specimens was more than twice as great as the number of x-rays. This occurred because most of the testing stations had only x-ray equipment and many persons who had x-ray films made at these stations subsequently visited other locations to have a blood sugar test. At testing stations where both chest x-ray and blood screening tests were available, an average of 55 per cent of participants took both. (In a more recent multiphasic screening program in Orange County, with adequate publicity and with two technicians collecting blood at each testing station, 94 per cent of participants received blood sugar tests.[16])

SECONDARY SCREENING TEST RESULTS

All persons with "positive" results in the primary blood sugar screening test (see Table 1) were asked to return for a secondary blood sugar screening test. In these tests 180 mg. of sugar per 100 cc. of blood was the screening level. Capillary blood was tested by the Wilkerson-Heftmann method. Persons previously known to have diabetes were tested without dietary preparation. Others reported in a fasting condition and were tested one hour after ingestion of 50 gm. of dextrose.

Secondary blood sugar screening tests were performed for 164 (86 per cent) of the 191 persons in whom diabetes was suspected. Results of these tests are presented in Table 3. Eighty-four (51 per cent) of the 164 secondary tests were "positive"—that is, indicated capillary "true blood sugar" values above 180 mg. per 100 cc. Among persons originally "positive" when screened at the level of 130 mg. of sugar per 100 cc. of blood, 59 or 48 per cent of 123 had "positive" results in secondary tests. Among those originally "positive" at 180 mg. per 100 cc., 25 (61 per cent) of 41 were "positive" in secondary tests.

Twenty-eight or 64 per cent of the 44 persons previously known to have diabetes who returned for a second test had blood sugar values above 180 mg. per 100 cc.

NEWLY DISCOVERED CASES OF DIABETES

It has been shown that there were 191 persons with "positive" results in primary screening tests among the 14,681 persons who stated that they did not have diabetes. More specific secondary screening tests were performed for 164 of these 191 persons. Sixty-four persons whose primary screening test was "positive" at the screening level of 130 mg. of sugar per 100 cc. of blood, but whose secondary screening test was "negative" were excluded from further consideration. Thus the number referred to their physicians with suspicion of diabetes was reduced from 191 to 127.

Diagnostic reports were received from physicians for 102 of the 127 persons referred with suspicion

TABLE 4.—*Diagnosis, Screening Level of Primary Screening Test and Result of Secondary Screening Test of Persons with "Positive" Primary Screening Test Who Were Not Previously Known to Have Diabetes*

Diagnosis	Total	Persons with Primary Test "Positive" at 130 mg. of sugar per 100 cc. of blood, Secondary Test: Pos.	Neg.	None	Persons with Primary Test "Positive" at 180 mg. of sugar per 100 cc. of blood, Secondary Test: Pos.	Neg.	None
Diabetes (newly discovered)	58	34	....	7	16	1	....
Not diabetes	44	20	....	4	6	10	4
Unknown	25	5	....	7	3	5	5
Subtotal	(127)	(59)	....	(18)	(25)	(16)	(9)
(Not referred to physicians)	64	....	64	....	....	....	....
Total	191	59	64	18	25	16	9

TABLE 5.—*Newly Discovered Diabetics by Primary Screening Level, Age Group and Sex*

Primary Screening Level (sugar per 100 cc. of blood)	Age Group	Number of Newly Discovered Diabetics			Per cent of All Participants Reported as Newly Discovered Diabetics		
		Total	Male	Female	Total	Male	Female
130 mg.	All ages	41	15	26	.56	.46	.64
180 mg.	All ages	17	8	9	.23	.24	.23
Total—Both Screening Levels—	Under 20	....	....	....	....	....	....
	20-29	3	1	2	.09	.07	.11
	30-39	7	2	5	.18	.12	.22
	40-49	14	7	7	.48	.50	.46
	50-59	22	8	14	1.14	.89	1.37
	60-69	12	5	7	1.15	.94	1.36
	70 & over	....	....	....	....	....	....
	All ages	58	23	35	.40	.35	.44

of diabetes (Table 4). The other 25 persons either did not seek medical advice or could not be traced. Fifty-eight of the 102 reports from physicians stated that the diagnosis was diabetes and that the disease was detected as a direct result of referral by the survey. These 58 newly recognized cases represent a diabetes discovery rate of 0.40 per cent. In other words, one out of every 250 participants in the blood sugar screening program was found to have previously unrecognized diabetes.

The diabetes discovery rate was relatively high in age groups above 50 and somewhat higher in females than males. Thirty-four of the 58 newly discovered cases of diabetes were found among the 2,972 participants aged 50 to 69, a discovery rate of 1.14 per cent. Twenty-four cases of diabetes were found among 11,709 other participants, a discovery rate of 0.20 per cent. Although the incidence of "positive" results in primary screening was considerably higher in males (see Table 2), the diabetes discovery rate was 0.35 per cent for males and 0.44 per cent for females.

It may also be seen in Table 5 that there was a large difference in the diabetes discovery rate with respect to primary screening levels. Among the 7,373 persons originally tested at the 130 mg. per 100 cc. blood sugar screening level, 41 or 0.56 per cent were subsequently found to be diabetic. Among the 7,308 originally tested at the 180 mg. per 100 cc. level, only 17 or 0.23 per cent were shown to be diabetic. If age-specific and sex-specific discovery rates of the former group are applied to the latter group, it is found that discovery of 36 instead of 17 new cases of diabetes might have been expected. It will be recalled that the primary screening level for each participant was determined by the answer to the question, "Did you eat or drink anything during the last two hours?" Incorrect affirmative answers would tend to lower the percentage of "positive" results at the 180 mg. per 100 cc. screening level whereas incorrect negative answers would tend to raise the percentage of "positive" results at the 130 mg. per 100 cc. screening level. There was no way of quantitatively determining the effect of incorrect answers on primary screening test results in this survey. It is apparent, however, that an appreciable number of unrecognized cases of diabetes escaped detection by the primary screening test at the 180 mg. per 100 cc. level. Greater sensitivity would have been achieved by using a lower screening level.

If screening levels of 130 mg. and 160 or 170 mg. per 100 cc. (instead of 130 mg. and 180 mg. per 100 cc.) had been used, the diabetes discovery rates in the two screening level groups would probably have been more nearly equal. Recently reported studies of blood sugar screening levels[7, 22] are not directly applicable to surveys of the type here described because they use different criteria for "fasting" and "postcibal."

Information as to whether patients were under regular medical supervision was obtained for 64 of the 68 persons previously known to have diabetes who had a "positive" result in the primary screening test. In ten cases information was obtainable only from the patient: Four stated they were under regular medical care and six that they did not visit physicians regularly nor did they consider it necessary to do so. In 54 cases information was obtained from physicians: 38 patients had been following medical advice with reasonable regularity and 16 who had lapsed from care visited their physicians at least once as a result of the survey.

FOLLOW-UP ONE YEAR AFTER SURVEY

Some of the persons who were referred to their physicians because diabetes was suspected, while not then diabetic, might be considered prediabetic.[9] The appearance of diabetes in this group during the year following the survey was therefore investigated. The 44 persons diagnosed as "not diabetic" immediately after the survey were asked by their physicians to report for glucose tolerance tests one year later. Glucose tolerance tests were also offered to the 25 per-

TABLE 6.—*Glucose Tolerance Tests of Possibly "Prediabetic" Persons, One Year After Diabetes Detection Survey*

Status at Time of Survey			Glucose Tolerance Tests One Year After Survey							
			Sugar Content of Blood (mg. per 100 cc.) at Stated Hours After Ingestion of 100 Grams Glucose							
Age and Sex	Primary Screening Level (mg. per 100 cc.)	Diagnosis Immediately After Survey	0	30 min.	1 hr.	2 hr.	3 hr.	Glycosuria	Acetonuria	Interpretation
67 M	130	Not diabetic	156	257	348	343	226	4 plus	Trace	Diabetic
53 M	130	Not diabetic	234	334	388	322	287	4 plus	Neg.	Diabetic
74 F	130	Not diabetic	226	286	336	302	210	4 plus	Neg.	Diabetic
58 F	130	Not diabetic	264	346	371	300	356	4 plus	Trace	Diabetic
56 M	130	Not diabetic	135	228	307	218	153	1 plus	Neg.	Diabetic
44 F	130	Not diabetic	165	295	348	187	124	2 plus	Neg.	Diabetic
28 M	130	Not diabetic	143	204	234	183	130	Trace	Neg.	Diabetic
65 F	130	Not diabetic	143	178	200	177	143	Neg.	....	Diabetic
70 M	130	Not diabetic	83	180	248	159	86	4 plus	Neg.	Diabetic
38 M	130	Not diabetic	98	169	201	157	98	Trace	Neg.	Diabetic
52 M	130	Not diabetic	130	204	274	152	100	3 plus	Neg.	Diabetic
61 F	130	Not diabetic	74	166	157	144	101	Neg.	....	Questionable
60 F	130	Not diabetic	135	174	183	130	84	Neg.	....	Questionable
69 M	130	Not diabetic	130	214	187	126	109	Neg.	....	Questionable
59 F	130	Not diabetic	130	185	191	113	117	Neg.	....	Normal
72 M	130	Not diabetic	100	167	189	100	72	Neg.	....	Normal
4 M	130	Not diabetic	85	114	125	100	101	Neg.	....	Normal
27 M	130	Not diabetic	109	187	157	78	70	2 plus	Neg.	Normal
46 M	130	Not diabetic	106	152	126	68	86	Neg.	....	Normal
42 M	130	Unknown	185	242	380	314	243	4 plus	Neg.	Diabetic
54 M	130	Unknown	162	284	258	210	184	4 plus	Trace	Diabetic
52 M	130	Unknown	104	174	217	109	74	Trace	Neg.	Questionable
53 M	180	Not diabetic	113	208	274	156	96	1 plus	Neg.	Diabetic
48 M	180	Not diabetic	122	234	256	130	78	3 plus	Neg.	Questionable
62 M	180	Not diabetic	126	182	191	117	87	Neg.	....	Normal
37 M	180	Not diabetic	113	236	182	98	96	Trace	....	Questionable
32 M	180	Not diabetic	109	160	139	78	87	Neg.	....	Normal
61 M	180	Not diabetic	84	157	166	77	50	Neg.	....	Normal
29 M	180	Not diabetic	122	174	156	70	92	Neg.	....	Normal
70 F	180	Unknown	320	420	515	400	470	4 plus	Neg.	Diabetic
38 M	180	Unknown	122	161	109	107	113	Neg.	....	Normal
15 M	180	Unknown	115	217	122	96	74	Neg.	....	Questionable

Note: Within each of the four screening level-diagnosis groups, glucose tolerance tests are arranged in order of descending 2-hour blood sugar values.

sons whose diagnoses could not be obtained at the time of the original survey. Standard three-hour glucose tolerance tests with a test meal of 100 gm. of glucose were performed for 26 of the former and for six of the latter. The Folin-Wu method was used. Results are shown in Table 6.

The standard glucose tolerance test is the most exacting and precise method now available for determining the presence or absence of diabetes in doubtful cases. In normal persons the fasting venous blood sugar value (Folin-Wu method) is below 120 mg. per 100 cc., does not rise over 200 mg. per 100 cc. and returns to 120 mg. or less in two hours.[1, 5] Duncan[5] considers tolerance curves indicative of diabetes if the two-hour value exceeds 130 mg. per 100 cc. and the clinical evaluation is in keeping with the diagnosis. In complicating conditions such as thyrotoxicosis he considers two-hour values up to 150 mg. "nondiabetic" if the three-hour value is below 120 mg.

Since complete clinical data are not available, the tolerance curves in Table 6 were evaluated by the following criteria:

Diabetic.....2-hour value over 150 mg. per 100 cc.

Questionable.....2-hour value 121 to 150 mg. per 100 cc. or peak value over 200 mg. per 100 cc.

Normal.....2-hour value not over 120 mg. per 100 cc. and peak not over 200 mg. per 100 cc.

Among the 26 persons tested who were reported by their physicians as "not diabetic" at the time of the survey, 12 had "diabetic" glucose tolerance curves one year later and five others had questionable curves. Among the six persons tested whose diagnoses at the time of the survey were unknown, three had "diabetic" glucose tolerance curves and two had questionable curves. These results clearly indicate the need for continued clinical observation of persons suspected of having diabetes. Diabetes eventually develops in a large proportion of such persons.[9]

DISCUSSION AND CONCLUSIONS

Blood sugar screening tests and minifilm chest x-rays constitute a practical combination for community-wide disease detection programs. Both procedures are highly acceptable to the public. The effectiveness of the diabetes detection tests was demonstrated by the discovery of 58 previously un-

recognized cases, a discovery rate of 0.40 per cent, as reported by physicians who performed follow-up examinations soon after completion of the screening tests.

Blood sugar screening tests, especially if performed without prior dietary preparation of subjects, will permit diabetes to escape detection in some cases. The procedures used in this survey yielded discovery rates of 0.56 per cent for persons screened with 130 mg. of sugar per 100 cc. of blood used as the dividing line between "negative" and "positive," and 0.23 per cent for those screened at 180 mg. per 100 cc. The former had not eaten during the two hours preceding the primary screening test. The discovery rate in the latter group was deficient. It is recommended that in future surveys persons who have eaten within two hours be screened at a blood sugar level lower than 180 mg. per 100 cc.—at 160 or 170 mg. per 100 cc. This is considered a more practical approach than efforts to have large numbers of persons eat specified test meals or to obtain detailed dietary histories.

Publicity and community organization are essential to obtain participation of large segments of the population in screening programs. Information concerning the entire program rather than only one segment of it should be given. A community-wide educational program on diabetes was not possible in Contra Costa County because the blood sugar screening tests were available at only a few of the testing stations.

In 15 of the 32 cases in which glucose tolerance tests were performed on diabetes suspects one year after the survey, the results were interpreted as indicative of diabetes. Results in seven cases were considered questionable, and in ten were normal. These findings emphasize the need for careful and prolonged observation of diabetes suspects.

The 58 persons in whom diabetes was diagnosed immediately following the survey plus the 15 found to have diabetic glucose tolerance curves a year later make a total of 73 newly discovered cases of diabetes, a discovery rate of 0.50 per cent. This rate is approximately five times as great as the discovery rate for active tuberculosis in this survey.

The success of this combined diabetes detection and chest x-ray survey suggests that other screening procedures should be studied to determine whether it would be desirable to add them to similar programs.

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Chemical Agents in Neoplastic Diseases

An Evaluation of Chemotherapeutic Substances for Clinical Management

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• The rapid appearance of many new chemical substances which possess some antineoplastic effects has created a complex problem for the practicing physician. These agents which have shown promise in man and lower animals are grouped according to their modes of action. Each substance is discussed thoroughly with regard to its structure, activity, and influence upon the neoplasms of man. Key references are cited, and the practical value of each chemical agent is defined. The proper methods of administration of the compounds recommended for use are carefully described. In addition a section on agents whose therapeutic value has been disproven is also included.

THE THREE BASIC AIMS of chemotherapeutic agents for neoplastic diseases are to cure, to arrest, and to palliate.[7] No chemotherapeutic agent to date has been found to cure any neoplastic disease. The cure of cancer today rests with surgical or roentgen therapy. Therefore, the agents to be discussed are either arrestive or palliative. It must also be emphasized that a given agent may arrest specific neoplasms and yet be only palliative or even totally ineffective for others. Similarly, agents ineffective when given intravenously may temporarily arrest some tumors when used topically, intra-arterially or by other modes of administration. The point of attack upon the cancer cell has many approaches and the possibilities of favorably altering these avenues of entrance into the intrinsic mechanism of neoplastic cells may materially enhance the action of substances which are currently ineffective.

The number of chemical agents which have shown some activity against neoplastic diseases has increased considerably in the past ten years. Few of these agents have had extensive clinical trial. Studies of many in animal experimentation have only recently been completed and the clinical experience is encouraging but certainly not conclusive. Of all the compounds listed, nitrogen mustard (HN_2), colchicine, urethane, arsenic, the diamidines, antimony and the endocrines are readily available. These and the remaining substances are under active employment. These latter agents must remain in the investigative stage until the evidence gathered in patients can be thoroughly evaluated for toxicity, effectiveness and possible late, untoward reactions.

The agents have been grouped relative to their alleged mode of action or origin to assist physicians in gaining some insight for proper selection of the substances in the management of some neoplastic diseases (Table 1).

I. RADIOMIMETIC AGENTS

1. *Nitrogen mustards: Beta-chloroethyl amines (HN_2 and HN_3).* Over 600 congeners of methyl-bis (Beta-cholorethyl) amine (HN_2) have been prepared[119, 22, 80, 81] but none have been shown to possess any significant therapeutic advantage over HN_2 or HN_3.[81, 135, 158] In many institutions, HN_2 is administered in doses of 0.1 mg. per kilogram of body weight daily for three or four consecutive days in strict adherence to the early recommendations concerning its use.[119, 22] The administration of the total dose per kilogram of body weight in one single dose is equally effective, simpler and less traumatic to the patient since the nausea and vomiting following the HN_2 occurs only once and not three or four times as with the divided dose schedule.[14]

The material is best given into the stream of a rapid infusion of isotonic saline solution (Figure 1). The infusion should be started with a large bore needle (No. 18) to ensure a constant full stream of saline solution runnning rapidly when the HN_2 is injected into the stream through the rubber tubing attached to the needle. The HN_2 should be dissolved in isotonic saline solution, 10 cc. per bottle (10 mg.), reaspirated into a Luer-Lok® syringe and administered as rapidly as possible after solution. A No. 18 needle permits rapid mixing, but the injection into the saline infusion stream is best accomplished with a No. 25 or No. 26 needle. This technique minimizes or prevents thrombosis of the vein because the HN_2 is well diluted by the large volume of the saline infusion and does not irritate the vein.

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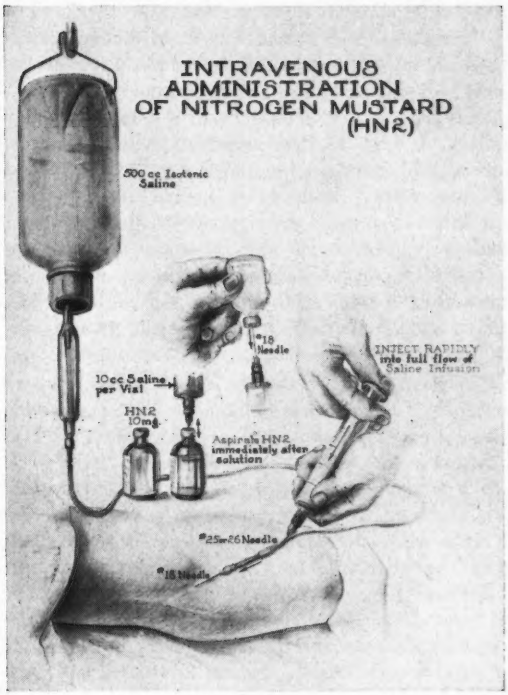

Figure 1.—A method of safe administration of agents which otherwise might cause venous thromboses. No. 18 needles are employed for rapid infusion of saline solution and for solution and transfer of the chemical. The smaller needle (No. 25 or No. 26) prevents too rapid administration.

The toxic effects of HN_2 are mainly those of depression of the hematopoietic tissues.[79] In patients with normal hematopoiesis, doses of 0.3 mg. per kilogram of body weight may be given at four- to six-week intervals for four to six months since the dearth of leukocytes is greatest 10 to 14 days following HN_2 and usually the number of leukocytes returns to normal within 20 to 25 days after administration.[14] In patients with impaired hematopoietic function, the intervals at which HN_2 may be readministered must be determined by frequent hematological study. It is advisable to count the leukocytes and platelets three times each week and the erythrocytes weekly until the count returns to normal. Occasional patients have pronounced sensitivity to HN_2 characterized by extreme nausea and retching, generalized erythema, and exhaustion. A generalized maculopapular eruption similar to that described by Zanes[170] has also been observed. A distinct conditioned reflex develops in some patients so that nausea and retching will occur *prior* to administration if the HN_2 is prepared in the presence of the patient.

Although the leukocyte count frequently falls to and below 1,000 per cu. mm. of blood following the repeated administration of HN_2 intravenously, the original fears of fulminating infections during the agranulocytic period have not been realized. The thrombocytopenia, however, is of more serious consequence. Patients may be permitted to be ambulatory with the leukocyte count fluctuating between 1,500 and 4,000 cu. mm. provided they are carefully

TABLE 1.—*Agents Under Investigation for the Treatment of Neoplastic Diseases*

I. RADIOMIMETIC AGENTS
1. Nitrogen mustards: Beta-chloroethyl amines (HN_2 and HN_3)
2. Triethylene melamine: Trisethylene-imino-s-triazine (TEM)
3. R-48: Beta-naphthyldi-2-chloroethyl amine
4. Hemi-sulfur mustard: 2-chloro-2′-hydroxydiethyl sulfide (HSM)

II. MITOTIC INHIBITORS
1. Colchicine
2. Podophyllin and Podophyllotoxin
3. Peltatins
4. Urethane: ethyl carbamate
5. Arsenic: Potassium arsenite (Fowler's solution)

III. SUBSTANCES TOXIC TO CELLS
1. GT-41: 1,4,dimethane sulfonoxy butane
2. Diamidines: Stilbamidine and Pentamidine
3. Alloxan: Mesoxyl urea
4. Antimony

IV. ANTIMETABOLITES
1. Folic acid antagonists: 4-amino pteroyl-glutamic and aspartic acids
2. Adenine antagonist: 2,6-diaminopurine
3. Guanine antagonist: 8-azaguanine
4. Pyridoxine antagonist: desoxypyridoxine
5. Para-amino-benzoic acid (PABA)
6. Riboflavin inhibitor: galacto-riboflavin and iso-riboflavin
7. Melanin antagonist: Mono-benzyl ether of hydroquinone

V. ENDOCRINE SUBSTANCES
1. Androgens: Testosterone propionate, methyltestosterone and methylandrostenediol (MAD)
2. Estrogens: Stilbestrol, estradiol and related compounds
3. Progesterone
4. Corticotropin (ACTH)
5. Cortisone: 17-hydroxy-11-dehydrocorticosterone (Compound E)
6. Para-hydroxy-propiophenone

VI. BIOLOGIC AND BACTERIAL PRODUCTS
1. Shear's polysaccharide
2. Lymphokentric and myelokentric acids
3. Rabies vaccine

VII. AGENTS OF RECENT INTEREST WHOSE EFFECTIVENESS HAS NOT BEEN SUBSTANTIATED TO DATE
1. Krebiozen
2. ACS—Antireticular cytotoxic serum
3. K-R: Klyueva-Roskin vaccine
4. Chymotrypsin

and frequently observed, although antibiotics may be deliberately withheld until definitely indicated. If bleeding occurs, strenuous antihemorrhagic measures should be initiated.

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3. *Peltatins:* Leiter, Downing, Hartwell and Shear[93] further isolated a group of compounds from crude podophyllin and then synthesized various related congeners whose action simulated that of podophyllotoxin. One group of related compounds, termed *peltatins*, was investigated by Greenspan, Leiter and Shear[53] in mice transplanted with various neoplastic diseases. These compounds produced specific alterations in tumor cells which resembled those obtained with colchicine. The chemical formulae of podophyllotoxin and the peltatins are quite similar. Later 45 patients with various neoplastic diseases received alpha-peltatin, 0.1 to 0.5 mg. per kilogram of body weight intravenously. Although a few instances of transient regressions of lesions were observed, they occurred at dose levels which produced toxic reactions.[52]

4. *Urethane: Ethyl carbamate.* Interest in the carbamic esters was revived by the studies of Templeman and Sexton[155] who confirmed the growth-suppressive findings of Lefevre.[92] Soon thereafter Haddow and Sexton[57] demonstrated that ethyl carbamate (urethane) produced profound histological changes in tumors in mice and rats. Urethane is preferably given with meals in enteric-coated tablets, in capsules or in liquid form. Parenteral administration remains experimental and cannot be recommended.

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tion or P^{32} therapy. The erythrocyte level usually remains unchanged although occasionally it will fall or, less often, rise. The platelet count is usually maintained.[6] Urethane may serve as a useful therapeutic agent in this disease in the absence of x-ray P^{32} or GT-41.

Rundles reported benefit in nine of 16 patients with widespread multiple myeloma who received one or more courses of treatments.[95, 127] The course of treatment was for eight to ten weeks in total doses of 120 to 290 grams in two months and repeated during an 18-month period for a total amount of 1,850 grams. Within two to four weeks after therapy was begun, skeletal pain and fever subsided, the hematological condition improved and the content of abnormal proteins in the serum became less or disappeared. Recalcification of widespread skeletal lesions has been observed in four to six months.[127] Accessible areas of skeletal involvement are best treated by x-radiation.

The exact mode of action of urethane upon neoplastic tissues is obscure but it has been reported that it is rapidly and completely metabolized within 24 hours and that the rate of breakdown is slower in tumor-bearing mice than in normal mice.[106] Urethane is a hematopoietic depressant and protracted daily administration can result in marrow hypoplasia with persistent leukopenia, thrombocytopenia and anemia. Gastric irritation with nausea and vomiting are common complaints with oral administration, but these conditions disappear promptly upon decrease in dosage or cessation of therapy. Blood studies at least twice each week are necessary for the proper control of therapy with this agent. The depression of the bone marrow elements is relieved slowly after cessation of therapy.

5. *Arsenic: Potassium arsenite (Fowler's solution).* Arsenic is employed most effectively as potassium arsenite (Fowler's solution) in doses of 15 to 30 drops per day in the treatment of chronic myelogenous leukemia.[42] Potassium arsenite inhibits mitosis at metaphase in a characteristic fashion similar to that of urethane but different from that of HN_2.[5] Since protracted arsenical therapy is hematopoietically depressant and cumulative, frequent hematological examination is necessary when this agent is employed.

III. SUBSTANCES TOXIC TO CELLS

1. *GT-41: 1, 4, dimethane sulfonoxy butane.* Following the demonstration that some sulfonic acid esters possessed radiomimetic activity,[18, 58, 161] Galton[44] reported the effectiveness of 1,4,dimethane sulfonoxy butane (GT-41) in myeloid leukemia. Three patients with chronic myelogenous leukemia were treated with 1,4,dimethane sulfonoxy butane, 8 mg. per day for four weeks for a total dosage of 200 to 250 mg. In all cases there was rapid clinical improvement during which the appetite was regained as well as strength, the enlarged spleen regressed in size, the hemoglobin rose and there was an accelerated decrease in primitive granulocytic leukocytes with an increase in mature forms in the peripheral blood.[44] GT-41 has been shown to reduce total leukocyte count, almost exclusively at the expense of the immature granulocytic forms. Accordingly, its clinical value lies in the hypercellular forms of chronic myelocytic leukemia. In the more fulminant forms of myelocytic leukemia with a preponderance of early immature granulocytes, the anemia and thrombocytopenia usually become progressively more severe despite a decrease in the leukocyte count. The effective dosage is 25 mg. daily for three to six days, and the decrease in leukocytes occurs within the next seven to ten days. Excessive dosage results in hypoplasia of the marrow with thrombocytopenia, anemia and leukopenia which may be fatal. Maintenance doses are difficult to establish.

2. *Diamidines: Stilbamidine and Pentamidine.* Stilbamidine® and Pentamidine® were introduced by Snapper[141] as therapeutic agents for multiple myeloma. Many interesting reactions of the diamidines with cellular nucleic acids were observed.[142] Clinical trials even in massive doses afforded temporary relief of bone pain in about half of the patients; the ultimate course of the disease was unaltered.[48, 59] The recommended course of parenteral therapy is 100 to 150 mg. every other day for 15 doses, repeated after a two-week rest interval, for a total of 4 to 6 grams over a period of four to five months. Rapid intravenous administration may produce hypotension, dyspnea, paresthesias and signs of impending shock. Electrocardiograms may show pronounced changes suggestive of myocardial ischemia if the injection is too rapid.[15]

Approximately 25 to 50 per cent of patients receiving intramuscular or intravenous Stilbamidine have paresthesias, and hypesthesias along the fifth cranial nerve distribution during or shortly after protracted treatment. These facial paresthesias have persisted permanently in some patients.[48] Pentamidine is claimed to cause facial neuropathologic change and other toxic manifestations less often than does Stilbamidine. Since x-irradiation and urethane have shown much more favorable effects, the use of these diamidines for multiple myeloma is limited. Diamidines are not considered preferable to conventional analgesics for the relief of pain and they are more likely to cause untoward side reactions.

3. *Alloxan: Mesoxyl urea.* Brunschwig and Allen[21] originally treated a patient with an islet cell tumor of the pancreas by intravenous administration of

alloxan.[34] Beneficial results with alleviation of frequent hypoglycemic episodes in that one case led to trials on other neoplasms and conditions with varying equivocal success.[21, 153] Other investigators[40] using alloxan intravenously in carcinoma of the pancreas did not observe favorable changes.

4. *Antimony:* Antimony has been used previously to influence the course of neoplastic diseases[3] and while the changes produced have not been dramatic, some alteration in the hematologic disorders have been reported.[97] More recently Rubinstein[125] employed Neostibosan® in the treatment of multiple myeloma with equivocal results.

The mode of action of antimony as a growth-suppressive is obscure but evidence indicates that it is closely related to that of arsenic.[51]

IV. ANTIMETABOLITES

The biological function of many essential metabolic substances may be antagonized by other compounds with closely related chemical structures. This antagonism between essential metabolites and their structural analogs may be utilized to interrupt specific cellular functions. In this manner sulfanilamide blocks the utilization of para-amino-benzoic acid by some bacteria, and scurvy can be produced in guinea pigs by the administration of gluco-ascorbic acid. Similar alterations in normal cellular enzyme metabolism may be produced by other vitamin analogs.[167]

1. *Folic acid antagonists.* Of the metabolic antagonists which have undergone animal or clinical trial, the 4-amino derivatives of folic acid have shown the most pronounced effects upon neoplastic diseases.[39] Three closely related substances, 4-amino pteroyl-glutamic acid (Aminopterin®), 4-amino N^{10} methyl pteroyl-glutamic acid (A-methopterin®) and 4-amino pteroyl-aspartic acid (Amino-an-fol®), have received extensive trial in the leukemias in the past four years. Aminopterin and A-methopterin have produced pronounced alterations in the hematopoietic tissues with temporary remissions in 20 to 30 per cent of children with lymphatic leukemia.[36, 37, 145, 157] The severe toxicity so frequently encountered with small to moderate amounts of these antagonists often necessitates discontinuance of the therapy.

The folic-acid antagonists are usually administered orally or intramuscularly in doses determined specifically for each patient. The usual dose of Aminopterin for children is 0.5 to 1.0 mg. daily; for A-methopterin it is 2 to 5 mg. daily in children and 5 to 10 mg. in adults parenterally or by mouth. For amino-an-fol it is 30 to 75 mg. per day intramuscularly—the smaller doses for children, the larger for adults. Adults tolerate Aminopterin less well than children on the basis of body weight. The dosage usually is gradually reduced and continued until manifestation of toxicity appears. Clinical improvement usually appears during the initial phases of the bone marrow depression. Macrocytosis, megaloblastosis and multilobulation of the neutrophils have been observed with small doses during Aminopterin therapy of leukemia in man and animals[76, 156] and have been attributed to the production of folic acid deficiency.[78] Hematopoietic depression of the blood and marrow elements may progress to complete aplasia if the dosage is not discontinued or promptly reduced. If therapy is protracted, other more systemic toxic signs soon appear—ulcerations of the entire gastrointestinal mucous membranes from the mouth to the anus, associated with diarrhea, hemorrhage, weakness and anorexia. Alopecia and skin eruptions of many varieties may occur during therapy, but these conditions are ameliorated when use of the drug is discontinued.[24]

The acute signs and symptoms of toxic reaction to therapy with folic acid antagonists may be partly ameliorated by the administration of folic acid, or folinic acid (citrovorum factor).[143, 154, 166] Large doses of these substances will completely override the antagonist. In children the course of leukemia is most often rapid, and approximately 90 per cent of cases are of the lymphatic type.[11] The natural history of untreated lymphatic leukemia in children is characterized by a variable course of two to 16 months with an average of 5.6 months. Supportive therapy with blood and antibiotics will increase the average survival to 8.9 months. This is about equal to the mean life span of children treated with hormones or antagonists in addition to support with blood and antibiotics.[11]

In a four-year period, 311 patients with acute leukemia were treated with folic acid antagonists by the Farber group.[38] Of these, 243 were treated for three weeks or longer. Approximately two-thirds of the 243 are reported to have responded favorably to these compounds. The mean survival of the 311 patients was calculated to be nine months. However, of the patients treated for three weeks or longer, 58 or 18.6 per cent survived more than 12 months; 39 or 12.1 per cent survived more than 15 months; 26 or 8.3 per cent more than 18 months, and seven or 2.2 per cent more than 29 months. Of the seven who lived more than 29 months, five were alive at the time of report. With the exception of the five living children, the remainder of 243 patients treated for three weeks or longer sooner or later reached a point at which the folic acid antagonists were no longer effective. The citrovorum factor had no value in the prevention or treatment of toxicity which could not be equalled by careful administration of the antagonists alone.

Farber and co-workers reemphasized that the remissions were temporary, that the compounds were

toxic, that there was no evidence that would justify the term "cure" of acute leukemia in children, and that value of these compounds is still limited to research. However, it must be considered that definite prolongation of life occurred in some members of the group treated. Both intermittent and continuous administration of the antagonists have been employed and in some instances the addition of corticotropin (ACTH) or cortisone to the regimen has been of great aid as concerns the comfort of the patients, and perhaps in further prolongation of life.[69, 120]

2. *Adenine antagonist: 2,6-diaminopurine.* Burchenal and co-workers[23, 25] studied an adenine antagonist, 2,6-diaminopurine, and found this compound to prolong the life of leukemic mice. Clinically, however, the drug was inconsistent in action and ineffective when employed in patients with acute leukemia.

3. *Guanine antagonist: 8-azaguanine.* Similarly 8-azaguanine (Guanazolo®), a guanine antagonist, was ineffective in clinical trials although it inhibited a mammary carcinoma EO771 in mice.[4, 86] This compound when administered orally to patients with various neoplastic diseases in doses of 50 to 100 mg. per day for 10 to 14 consecutive days caused diarrhea and marked erythematous excoriations of the skin.[4]

Combined treatment with Guanazolo plus Aminopterin, Guanazolo plus alpha-peltatin, and Aminopterin plus alpha-peltatin had an additive inhibitory action upon a transplantable mouse leukemia (lymphoma 1210), without extra toxicity.[49, 50] Combinations of 8-azaguanine with an antiriboflavin compound or with stilbestrol caused tumor inhibition in mammary adenocarcinoma of mice.[43, 132]

4. *Pyridoxine antagonist: Desoxypyridoxine.* In mice and rats, inhibition of growth of transplantable tumors while the animals were receiving pyridoxine-deficient diets was observed.[87] The addition of desoxypyridoxine to the deficient diet slowed the growth of a transplanted lymphosarcoma in mice.[146] Clinical trials in acute leukemia and lymphosarcoma, however, were without favorable effect.[47]

5. *Para-amino-benzoic acid (PABA).* Zarafonetis and co-workers[171] found that leukopenia occurred following protracted administration of large doses of para-amino-benzoic acid and that it was relieved promptly upon cessation of therapy.[172] High content of the drug in the blood can be maintained with doses of 2 to 4 grams every two hours. Profound and consistent but transient hematopoietic effects were observed in chronic myelogenous leukemia more frequently than in chronic lymphatic leukemia.

6. *Riboflavin inhibitors: Galacto-riboflavin and Iso-riboflavin.* Galacto-riboflavin and Iso-riboflavin will suppress the growth of some animal tumors on riboflavin-deficient diets both in vitro and in vivo.[35, 147]

7. *Melanin antagonist:* Mono-benzyl ether of *hydroquinone.* Oliver and co-workers[111] reported the depigmenting properties of a compound while studying the cause of skin changes in workers from a commercial rubber manufacturing plant. The causative material, mono-benzyl ether of hydroquinone, interferes with the normal melanin metabolism. Hence it was employed in investigations to influence malignant melanomas. Kelly and co-workers[85] treated nine patients with malignant melanoma with large oral doses of this substance. The patients were closely observed and chemical and cytologic studies of the blood and examination of biopsy material were carried out frequently. No significant or consistent favorable alteration of the natural course of the disease was observed.

V. ENDOCRINE SUBSTANCES

Hormonal therapy of advanced mammary cancer is arrestive or palliative but not curative under any conditions.[54, 107, 163] Only five types of neoplastic disease are altered by hormonal therapy—lesions of the breast, prostate, uterus, lymphatic and hematopoietic systems. Roentgen therapy is most advantageous for arrest or palliation when metastases are localized and accessible yet beyond the scope of surgical treatment.[45] Hormonal therapy is preferable for widespread soft tissue, visceral or osseous metastases.

Approximately 25 per cent of patients with advanced neoplastic involvement from carcinoma of the breast will benefit objectively from therapy with estrogenic or androgenic hormones.[30, 107] Extensive clinical experience has been attained with two androgens, testosterone propionate and methyltestosterone, and with six preparations of estrogens, diethylstilbestrol, ethinyl estradiol, estradiol dipropionate, dienestrol, dimethyl ether of diethylstilbestrol and Premarin.® Postmenopausal women respond much better to estrogens than premenopausal women, and the best results are obtained in patients who are more than five years postmenopausal. The functional state of the ovaries apparently has little effect on the response to testosterone propionate. In the premenopausal and menopausal patients, estrogens and androgens are about equally effective in soft tissue lesions resulting from carcinoma of the breast, but in postmenopausal patients estrogens are superior to testosterone propionate. Occasionally acceleration of the disease occurs during hormonal therapy, most frequently in the menopausal or premenopausal patients receiving estrogens. Therefore, castration (if not contraindicated) and androgens are the treat-

TABLE 2.—*Steroid Hormones of Value in the Treatment of Advanced Mammary Cancer*

	Route	Dose schedule preferred: Mg.	Daily	Weekly	Minimal total dose
ANDROGENS:					
Testosterone propionate	Intramuscular	50-100		3	3 gm/3 mo.
	Buccalet	40- 60	1		3-5 gm/3 mo.
Methyltestosterone	Oral	200	1		30 gm/6 mo.
Methylandrostenediol	Intramuscular	100-200		3	4-7 gm/3 mo.
ESTROGENS:					
Diethylstilbestrol	Oral	15	1		2-4 gm/3-6 mo.
Ethinyl estradiol	Oral	3	1		200 mg/3-6 mo.
Estradiol dipropionate	Intramuscular	5	2		200 mg/3-6 mo.
Dienestrol	Oral	15	1		4 gm/3-6 mo.
Dimethyl ether of diethylstilbestrol	Oral	30	1		4 gm/3-6 mo.
Premarin	Oral	30	1		4 gm/3-6 mo.
TACE (tri-para-anisyl chloroethylene)	Oral	24	1		Investigative stage: to be determined

ments of choice for soft tissue lesions in the premenopausal patient. Testosterone propionate is more effective than estrogens in relieving subjective bone pain although there is little difference, objectively, between the two steroids with respect to recalcification of the osseous lesions.

1. *Androgens: Testosterone propionate, methyltestosterone and methylandrostenediol (MAD).* Testosterone propionate, 50 mg. three times each week, intramuscularly, is as effective as the previously recommended dosage of 100 mg. three times each week. Daily, frequent dosage orally or by buccal absorption may be employed as an adjunct to intramuscular administration but the equivalent dosage must be absorbed, and this is usually more expensive by the oral than by the parenteral route.[30, 107] Pellet implantation permits uniform absorption of androgens or estrogens[16, 137] and in adequate amounts will often suffice for two to three months. Hormonal therapy should be continued until definite progression of the disease resumes. Cessation of therapy may then cause another regression; and regression may also occur if a change is made to another hormone. The response to the hormones is temporary. Each eventually becomes ineffective. Some investigators feel, therefore, that the hormones should be administered intermittently, preferably cyclically, and that furthermore they should be employed sparingly to avoid premature exhaustion of the therapeutic armamentarium. On the other hand other authorities feel the hormones should be continued as long as response is favorable.

Combined androgen and estrogen therapy in patients with advanced mammary cancer is at present under trial but conclusions cannot yet be drawn.

Recently, Homburger and co-workers[73] reported favorably on the effects of methylandrostenediol, an androgen said to exert the characteristic anabolic activity of testosterone without the masculinizing accompaniments.

Kasdon and co-workers[83] reported subjective improvement in 30 of 40 patients with advanced mammary cancer treated with methylandrostenediol (MAD) administered orally, subcutaneously and by pellet implantation. In nine of the 30 there was objective evidence of improvement. Hypercalcemia, the only major side effect observed, occurred in three patients with extensive osteolytic metastases. Segaloff and his associates[129] reported similar although not so encouraging observations in 24 cases. Only two of the patients, both with soft tissue lesions, had objective regression of lesions after intramuscular administration of 300 to 700 mg. of MAD per week. There was no beneficial effect on metastases in any patient in the series.

The dosage of this androgen is approximately twice that of testosterone propionate. There has been less clinical experience with methylandrostenediol than with the older testosterone preparations, but results of recent clinical investigations with this nonvirilizing androgen are encouraging.

2. *Estrogens.* The first six estrogens listed in Table 2 are considered to exert similar activity when given in equivalent dosage. Frequently, however, some preparations are better tolerated than others. Also, a change from the oral to the parenteral route of administration may significantly ameliorate the undesirable side effects. The fact that patients with metastatic mammary cancer respond similarly to either estrogens or androgens suggests a common metabolic utilization of these compounds.

More recently a new substance, Tri-para-anisylchloroethylene (TACE), has been reported as a potent estrogen without the undesirable feminizing side effects. Its value in the treatment of advanced prostatic cancer has been suggested[140, 152] but more clinical confirmation is needed before TACE can be recommended.

Patients with advanced carcinoma of the prostate can be benefited by the administration of estrogens.[60, 74, 109] In a study of 100 consecutive cases of

carcinoma of the prostate, Harrison and Poutasse[60] found that the most effective hormonal treatment of carcinoma of the prostate was orchiectomy combined with estrogenic therapy. Seventy per cent of patients with extensive carcinoma of the prostate had symptomatic and objective improvement with this form of therapy.

All known effective measures should be instituted as soon as possible. It is desirable to reduce the androgen predominance, and there is much controversy as to whether castration, or estrogen administration or both are the preferred courses of action. In general it is felt that orchiectomy followed by prolonged oral administration of 5 to 10 mg. daily of stilbestrol or an equivalent estrogen is most effective. Since the psychological barrier of orchiectomy often is difficult to overcome, many patients are treated with estrogens alone, often with good results. The estrogens may also be administered intramuscularly, or pellets may be implanted. Approximately 75 per cent of patients so treated show subjective and often objective improvement as judged by subsidence of pain, return of appetite, gain in weight and strength, decrease in size and hardness of the prostate, relief of urinary obstruction and roentgenographic evidence of disappearance of metastases to bones. Although the regressions are temporary, there is now evidence that definite prolongation of life has been achieved.

The toxic complications with estrogens—edema, hypercalcemia, menorrhagia and metrorrhagia—are related particularly to large doses given over long periods. At least eleven instances of carcinoma of the breast have occurred in men treated with estrogens for two or more years for carcinoma of the prostate, although the association has been contested.[26] Castrodale, Bierbaum, Helvig and MacBryde[27] noted pronounced hematological and hepatic changes following prolonged administration of estradiol and stilbestrol in dogs, characterized primarily by thrombopenia with fatal hemorrhages.

Frequently nausea and vomiting occur during estrogen therapy, and although these reactions may abate after one to two weeks of therapy it is often necessary to discontinue treatment because of them. Reducing the dosage, substituting other estrogens or changing to parenteral administration may alleviate gastrointestinal distress.

The toxicity of androgens is evident after protracted administration and large dosage. In women, masculinizing and other changes appear within a few weeks—changes such as hirsutism, hoarseness, increased firmness of the musculature, increased libido, amenorrhea, water retention and hypercalcemia.[30] Upon cessation of therapy these conditions gradually subside. A salt-poor diet will often prevent water retention.

3. *Progesterone.* Large doses of progesterone (250 mg. daily) intramuscularly are reported by Hertz[67] to be associated with a decrease in size, vascularity and friability of lesions of carcinoma of the cervix. The changes are not sufficient, however, to recommend progesterone as a therapeutic agent in carcinoma of the cervix at this time.

4. *Corticotropin (ACTH).* The pituitary adrenocorticotropic hormone is available in single sterile ampules of 25 mg. The dosage varies widely depending upon the desired goal. Intramuscular doses of 50 to 200 mg. per day in two or three divided doses are most commonly employed.[121, 159] Intravenous administration of corticotropin (20 mg. daily) is comparable to intramuscular administration of five to ten times that amount and is therefore more economical.[122] Slow infusion increases the adrenal cortical response to a given dose of the hormone. The side effects are analogous to those that occur when corticotropin or cortisone is administered by other routes.

5. *Cortisone: 17-hydroxy-11-dehydrocorticosterone (Compound E).* Cortisone is the name coined by Kendall to identify 17-hydroxy-11-dehydrocorticosterone, or "Kendall's Compound E."[102] Cortisone is considered a growth-suppressive.[35, 62, 143] In some cases of neoplastic diseases in which this material was used there were definite although mostly subjective, slight and transient effects.[66, 75, 116] The intramuscular dose ranges from 25 to 100 mg. per day, usually given once or twice a day. Oral administration is equally effective in identical doses if taken daily in three to four equally divided doses.[160] Corticotropin and cortisone probably reduce the tissue reaction to neoplasms with little or no favorable effect on the cancerous process itself.[159]

The effects and complications of corticotropin and cortisone are identical as far as can be ascertained today and are ascribable directly or otherwise to their metabolic or endocrine functions.[144, 159] It should be emphasized that corticotropin causes adrenal cortical hypertrophy and cortisone is associated with cortical atrophy. The unfavorable effects of corticotropin and cortisone occur with prolonged administration of large doses and are identical with the symptoms of hypercorticoidism (Cushing's syndrome)[1, 66, 144] which include impairment of carbohydrate tolerance, weakness and wasting of muscle, osteoporosis, striation of the skin, bruising tendency, rounding of the facial contours, acne, hirsutism, alkalosis, loss of gonadal activity, psychoses and hypertension.

Cortisone and corticotropin have been observed to produce striking changes in hematological dyscrasias.[159, 165] Favorable responses occur initially in about 50 per cent of patients with acute lymphatic leukemia, can seldom be repeated in the same patient

with repeated courses of therapy, and, as with other hormonal substances, loss of tolerance rapidly appears after the first or second course of therapy.

To attain therapeutic results in the lymphomas and leukemias the dosage often must be forced until at least some part of the Cushing syndrome appears. Most of this syndrome will regress quickly but often not completely following discontinuance of the therapy. The appetite which becomes voracious during corticotropin or cortisone administration will subside promptly upon cessation of treatment. Prolonged metabolic changes such as the development of diabetes mellitus, malignant or benign hypertension, peptic ulceration, cardiac failure and permanent psychotic changes have not been reported.[70] Corticotropin and cortisone may depress the natural immunological processes in infections, resulting in enhancement of susceptibility and increased severity.[84]

6. *Para-hydroxy-priopiophenone.* This material has been reported by Buu-Hoi to exert pituitary-like effects and in clinical trials it is stated to have brought about temporary remissions in the course of various neoplastic diseases.[41, 117] Preliminary trials with this material (H365) in this country have not given any indications to date that would confirm the findings of the French investigators.

VI. BIOLOGIC AND BACTERIAL PRODUCTS

1. *Shear's polysaccharide.* The occasional regression of neoplastic lesions following infections and the administration of Coley's toxin to patients with advanced neoplastic diseases stimulated interest in similar biologic products.[108] Shear and co-workers purified preparations from Bacillus prodigiosus (Serratia marcescens) and obtained a group of polysaccharides[133] containing phospholipid and nitrogen fractions which decreased with greater purification. The material was administered intravenously in doses of 5 to 15 micrograms. Within 45 to 60 minutes fever, leukocytosis and hypotension occurred, with shock and occasionally death.[20, 72, 110] Temporary tumor regression was observed occasionally, associated with transient clinical improvement. Creech and co-workers employed newer polysaccharide preparations with similar results.[32] The substance is pyrogenic in man and produces hemorrhages within the tumors of both mice and man. The effect of the polysaccharides is primarily upon the vascular supply, related to systemic toxicity, and not directly upon the tumor cells.[2]

2. *Lymphokentric and myelokentric acids.* In 1939, Miller, Wearn and Heinle[105] reported the isolation of crude substances from the urine of leukemic patients which stimulated myelopoiesis and lymphopoiesis in animals. They named these substances lymphokentric and myelokentric acids. Eight patients with lymphoblastic leukemia were treated with myelokentric acid with equivocal changes and a suggestion of partial remissions.[104] Swan and Zelman observed similar phenomena in a patient with acute lymphoblastic leukemia treated with myelokentric acid.[151]

3. *Rabies vaccine.* Two of twelve patients with malignant melanoma treated with rabies vaccine had some regression of metastatic nodules without microscopic cellular alterations.[113] A later report[68] indicated that eight of thirty patients had definite regression of metastases and the authors felt that the development of new metastases was also retarded.

VII. OTHER AGENTS OF RECENT INTEREST

1. *Krebiozen.* Krebiozen is a substance reported to be derived from the blood of horses which have been inoculated with a stimulating material the nature of which has not been disclosed as yet.[77] By another process (also undisclosed) approximately 1.0 mg. of a white powder is obtained which is then diluted in distilled water for intramuscular administration. Although it has been specifically stated that Krebiozen is not antireticular cytotoxic serum (ACS) the approach is quite similar.[17] Extensive studies on neoplasms in mice, rats and dogs treated with Krebiozen by the Chicago group elicited no objective evidence of any effect upon these tumors.

Initial investigations upon 22 patients with various neoplasms were stated to show decrease in size of a lymphosarcomatous lesion in the breast of a 52-year-old woman and some decrease in nodes of a patient with Hodgkin's disease. Changes in the remaining 20 patients[77] were within the natural variation of neoplastic illnesses.

In studies in other laboratories on the use of Krebiozen in 100 patients with a wide variety of neoplastic diseases, no significant alteration in the course of the disease was noted in 98 cases.[31] In the other two patients transient changes occurred which were considered significant but within the natural variation of the specific disease. It must be concluded that the substance termed Krebiozen has not to date been shown capable of favorably influencing the neoplastic diseases studied, that the original claims concerning Krebiozen are without substantiation[31, 123, 164] and that the material cannot be recommended for use as a tumor chemotherapeutic agent at this time.

2. *Antireticular cytotoxic serum (ACS).* Bogomolets and his associates[17, 101] obtained a material from the blood of horses following the injection of human spleen and bone marrow tissue which, they reported, caused disappearance of metastases in lymph nodes and prolongation of life in inoperable cancer. The

substance was termed antireticular cytotoxic serum (abbreviated to ACS) and was proposed as an adjunct in the therapy of cancer to prolong useful life by causing regression of metastases, alleviation of pain and increase of appetite.[17] In neither clinical nor animal investigations in this country have such specific effects been observed upon benign or malignant tumors in mice, rats or man.[33, 63, 64, 65, 139]

3. *K-R: Klyueva-Roskin vaccine.* This water soluble, heat-stable endotoxin derived from Trypanosoma Cruzi was reported to cause regressions in both animal and human neoplasms.[89] Although a report by Malisoff[100] contained favorable implications, other more intensive studies by Cohen, Borsook and Dubnoff[28] in vitro and by Hauschka in vivo[61] in mice did not confirm the original claims. No reports upon this material have appeared recently.

4. *Chymotrypsin.* Independent clinical investigations by two groups[134,162] employing chymotrypsin[91] have failed to confirm the original claims made by Krebs and co-workers.[55, 90] Serious reactions were observed in four of ten patients treated over a protracted period, one of whom almost died following anaphylactoid reaction to an injection. No further authentic substantiation of the claims made for this material have appeared since. Chymotrypsin cannot be recommended as an effective agent for tumor chemotherapy.[29]

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A Change in VA Report on Patients

VETERANS ADMINISTRATION'S monthly "Statistical Summary of VA Activities" no longer distinguishes between non-service and service connected patients in VA hospitals. Previous summaries indicated that approximately two-thirds of the patients were non-service connected cases, but the current summary gives no indication what percentage of the 98,517 patients are in this category.—*From the A.M.A. Capitol Clinic.*

CASE REPORTS

- **Anterior Sacral Meningocele**
- **Scleromalacia Perforans**
- **Perineal Myoma**

Anterior Sacral Meningocele

JOHN D. BRIGGS, M.D., and
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ANTERIOR SACRAL MENINGOCELE is a herniation of the meninges through an anterior defect of the sacrum, forming a cyst-like structure filled with spinal fluid which is continuous with the subarachnoid space of the spinal cord. Fewer than fifty cases have been reported in the literature since the original description of this congenital anomaly by Bryant in 1837 (cited by Coller and Jackson[2]). In many of the reported cases, meningitis followed surgical procedures directed at the diagnosis or treatment of the lesion.

CASE REPORT

A 36-year-old white male mail carrier was admitted to the Veterans Administration Hospital, Los Angeles, September 22, 1948, with complaint of a tumor in the rectum. Five weeks before admittance he fell from a ladder and, in the belief his "coccyx was broken," two days later consulted a physician who noted a non-tender, spongy mass between the rectum and sacrum. He was examined by another physician who was unable to arrive at a definite diagnosis but advised incision and drainage in the belief that the lesion was either a hematoma or an abscess. For the preceding several months the patient had noted slight, sharp, stabbing pain associated with defecation. No material drained from the rectum and no bloody or tarry stools were passed.

Ten years before admittance the patient had had an injury to the left hip, and x-ray films of the pelvis were taken at that time. The films were not available but the report stated: "There is deformity of the distal end of the sacrum with absence of the coccyx and lower sacral vertebrae forming a half-moon shaped border. This is probably congenital but could be postoperative formation and is merely noted as being present."

Upon physical examination, the only abnormalities noted were in the rectum. There was a smooth, firm, non-tender, rubbery, rounded mass, 8 to 10 cm. in diameter, palpable between the rectum and the hollow of the sacrum. No pulsation was felt and no bruit could be heard on auscultation. In proctoscopic examination the mass was observed to be encroaching on the lumen of the rectum. The overlying mucosa was not involved. No neurological abnormalities were noted.

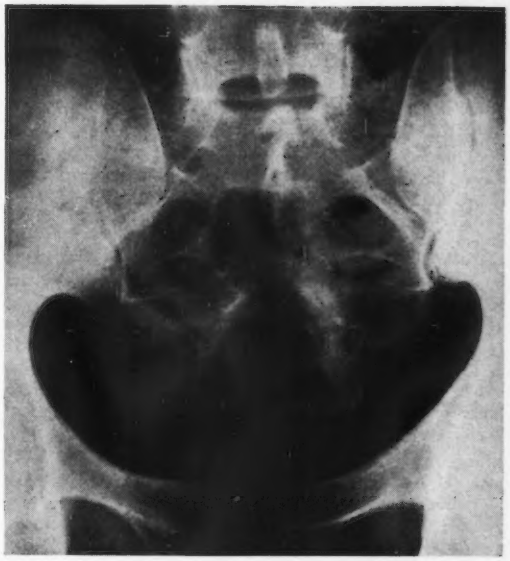

Figure 1. — X-ray of the pelvis showing the typical "scimitar" apearance of the sacrum with absence of the coccyx.

Results of examination of the blood, of urinalysis, and of a serological test for syphilis were within normal limits. No abnormalities were noted in an x-ray film of the chest. In roentgen studies with a barium enema, slight deviation of the pelvic colon was noted, and in a film of the pelvis congenital absence of the lower portion of the sacrum and coccyx was observed (Figure 1).

The diagnosis was still in doubt when the patient was taken to the surgery for excision of a biopsy specimen from the mass. Spinal anesthesia was used and the specimen was obtained through an incision in the midline, cephalad from the anus. A clear fluid was aspirated from the mass, and as it was withdrawn the tumor decreased in size as determined by rectal palpation. The incision was closed without placement of drains.

In microscopic examination of the aspirated fluid, 6 erythrocytes and 2 lymphocytes per cubic millimeter were noted. The fluid contained no globulin; the sugar content was 76

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mg., total protein, 29 mg. and chlorides 610 mg. per 100 cc. Results of Wassermann and gold curve tests for syphilis were negative.

The wound healed satisfactorily and the patient was discharged without further treatment.

When the patient was last observed, September 11, 1951, the symptoms were essentially the same as at the time of admittance three years before, and the meningocele did not appear to have increased in size.

DISCUSSION

The symptoms of anterior sacral meningocele are primarily owing to the mechanical effects of a pelvic tumor. Constipation and pain on defecation often are present. Serious obstetrical problems may arise because of partial occlusion of the birth canal. Occasionally minor nerve defects may be associated with the condition. Frequently symptoms are not pronounced and the tumor is found unexpectedly, as in the case presented here. Other congenital defects are often associated with this lesion.[3] Tumors of this kind occur more often in females than in males.

The diagnosis should be suspected when a tumor of the posterior pelvis is associated with a sacral defect. Sherman, Caylor and Long[5] observed that there were sacral defects in 23 of the 34 cases they reviewed. In many of the older reports, roentgen examination was not made and a sacral defect may have been present but overlooked. In the absence of a demonstrable sacral defect, the diagnosis must be confirmed by a myelogram or by aspiration of the tumor. It is important that aspiration or incision of the mass not be made through the rectum or vagina; meningitis developed in all of nine patients in the cases in which entrance was made by those routes, and seven of them died.[6] In the present case, unfamiliarity with the lesion was the reason for inability to make the proper diagnosis without surgical exploration and aspiration.

Surgical procedures performed in the diagnosis and treatment of these lesions have been accompanied by a high mortality rate. A course of "skillful neglect" has been advised, with the performance of cesarean section if sacral meningocele occurs as a complication of pregnancy.[5] Surgical ligation of the pedicle, which is often quite small, as it emerges through the sacral defect has been performed successfully several times and is the procedure of choice if it is decided that surgical removal is indicated.[1, 2, 4, 6] The removal of the sac is optional since it does not secrete spinal fluid. The posterior approach to the lesion is attended with fewer hazards and complications. Since the patient in the present case had minimal symptoms which did not increase in three years, surgical excision was not carried out.

SUMMARY

A case of anterior sacral meningocele is presented.

The dangers associated with methods of approach that are not strictly aseptic, either for diagnosis or treatment of this rare lesion, are outlined.

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Scleromalacia Perforans

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DISEASES OF THE SCLERA are among the most serious diseases of the eye because of the complications which may occur.

Classification of the diseases of the sclera is made upon anatomic and clinical observations because knowledge of what causes them is limited. The case here reported was particularly hard to classify. It could not be placed in a textbook classification until several months after onset. Even then all the facts did not completely fit into place. The rarity of the various forms of scleritis makes it important that each case be thoroughly studied and reported, in the hope that sufficient information will be amassed in the literature to permit significant etiological conclusions.

Frequently observed is the disease entity nodular episcleritis,[1] and occasionally a form of superficial scleritis called by Fuchs episcleritis periodica fugax. The former is described as a chronic recurrent nodular inflammation of the episcleral tissue, usually bilateral. The latter and more regularly recurrent form is considerably more diffuse with edema and congestion of the tissues which is not present in the more benign cases. These superficial forms are not understood etiologically any better than the deep forms, but they rarely constitute a threat to the eye.

Deep scleritis has been divided clinically into anterior and posterior scleral inflammations. All cases of scleritis are chronic in character and in many one or more complications develop, such as sclerosing keratitis, and/or uveitis with sequelae such as anterior and posterior synechia, iris bombe, vitreous exudates, choroiditis, secondary glaucoma and panophthalmitis. Each complication may gravely threaten the sight and even the retention of the globe itself.

Posterior scleritis is usually associated with tenonitis and is most often secondary to retrobulbar infection extending from the sinuses. The chemosis and frequent concomitant occurrence of retrobulbar neuritis are so severe that not infrequently enucleation becomes necessary.

Anterior scleritis occurs as one of four separate clinical entities: Annular scleritis, scleroperikeratitis, brawny scleritis and scleromalacia perforans. Duke-Elder[1] described these diseases as separate and not necessarily related diseases. Indeed, each has definite characteristics not present in the others. These characteristics may be found, however, to be only the special reactivity of the area involved and probably have nothing whatever to do with etiologic factors. Proper reclassification of these diseases clinically must await further pathologic and physiological studies.

Annular scleritis is usually a diffuse induration of the circumference of the anterior segment of the sclera; that is, that portion of the globe in front of the equator. There are usually present pin-head sized, hard, white nodules in the sclera. Necrosis is unusual on a gross scale but it may be

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noted in microscopic examination of an enucleated eye. Scleritis of this type is frequently followed by or associated with deep infiltrations in the cornea, and when this occurs the disease is called scleroperikeratitis.

Brawny scleritis is a much more virulent disease clinically. The sclera, episclera and conjunctiva take on a brawny, gelatinous appearance. There is a true pitting edema of the globe. Never in a case of this type has degeneration been reported to have extended posteriorly beyond the equator. Histologically, degeneration is found in the sclera but nodules are not present and ulceration does not occur.

Scleromalacia perforans was first described as a specific disease by Van der Hoeve[9] in 1931, and in 1934[10] he reported four cases in which characteristic holes occurred in the sclera. These holes developed slowly. Occasionally a yellow nodule appeared which, upon puncture, exuded a yellow granular detritus. Three of the four cases occurred in association with polyarticular rheumatism.

Smoleroff[8] reported the presence of areas of focal necrosis of the sclera in three cases of rheumatoid arthritis.

Edstrom[2] reported a case in which flat grayish nodules occurred in the sclera. The nodules consisted of granulomatous tissue with necrotic connective tissue in the center. Results of culture and guinea pig inoculation of material from the nodules were negative for tuberculosis. The patient had severe arthritis, and the result of an agglutination test was positive for a hemolytic streptococcus.

Up to 1938 there had been 14 cases reported with several others of questionable classification. Verhoeff and King[11] added a case to this list and reviewed all the preceding cases from the available information. They formulated a composite clinical description as follows:

> The disease may occur in one or both eyes simultaneously or at intervals in patients in the 5th, 6th and 7th decades of life. Present usually are slightly elevated nodules which involve the sclera and overlying tissues. These nodules may occur in the sclera from the limbus to the equator. The congestion is most often only moderate and is limited to the nodules and their immediate vicinity. After several months the nodules regress, leaving shallow concavities. When the nodule is at the limbus it may perforate into the anterior chamber. Actual rupture of the globe is uncommon. Evidence of intraocular infection is slight unless purulent infection occurs. Posterior synechia or cataract may develop. In most cases rheumatoid arthritis exists at the onset of scleritis.

In most cases the disease is associated with rheumatoid arthritis, but not in all. Oast[7] reported a case which was identical clinically and pathologically with the case described by Verhoeff but in which there was no arthritis.

REPORT OF A CASE

A 59-year-old Mexican male whose right eye had become inflamed three weeks previously was first examined in June 1949. He was illiterate, lived out of town and returned irregularly to the outpatient department for treatment. Mild injection of the bulbar and palpebral conjunctiva of the right eye was noted. No discharge, follicles or papillae were observed and no preauricular adenopathy was present. There were a few pin-point areas of staining on the right cornea. The ocular media were all clear and both fundi were normal. The visual acuity was 20/70 in the right eye and 20/30 in the left. Each eye was correctible to 20/20 with concave lenses. No evidence of scleral disease was noted on gross or slit-lamp examination. No other significant abnormalities were observed in a complete physical examination.

The eye was treated with 30 per cent sulfacetamide solution locally for two weeks without improvement. After two weeks (five weeks after the right eye was affected) the left eye became involved. During the first week that both eyes were involved some episcleral injection developed in an area 6 to 8 mm. wide surrounding the whole circumference of the limbus in both eyes. The ocular media remained clear and the vision was not diminished. A tentative diagnosis of episcleritis was made and the patient was given salicylate therapy and local application of heat.

The patient returned to the clinic July 5 because of increased pain and tenderness in each eye. There was a 2 mm. by 4 mm. punched-out ulcer in the indurated conjunctival tissue at the 12 o'clock position in each eye. These ulcers had a yellow necrotic base and extended to the cornea. The patient stated that the ulcers had been preceded by yellow nodules. He was hospitalized for further study.

No new information regarding the eyes was elicited by detailed questioning. The patient had been in good general health until two years previously. During this two-year period he had received intermittent therapy by his family doctor for pain in the ankles, knees and shoulders. Salicylate treatment in large doses for arthritis had been given for two months prior to the onset of the eye disease, but had caused so much gastric upset that it had to be discontinued.

Except for the eyes, no abnormality was noted in physical examination. There was no swelling, tenderness or limitation of motion of the joints. Results of all laboratory tests at the time of admittance, including serologic tests for syphilis, were within normal limits. No evidence of disease was noted in an x-ray film of the chest. The uric acid content of the blood was 4.2 mg. per 100 cc. The reaction to a skin test with 0.01 mg. of old tuberculin was negative at the end of 72 hours, and to 0.1 mg. of the substance was 1 plus in 48 hours. The result of a Frei test was negative. Coagulase-negative staphylococci were noted in smears and cultures of material from the conjunctiva of each eye, but no abnormal cells were seen on smears. Normal conjunctiva covering a non-specific granulomatous process was observed in biopsic specimens taken from each ulcer.

X-ray films of the knees and ankles showed slight irregularity of both malleoli and some hypertrophic fringing, of long duration, of the margins of the articular surfaces of the tibial spines of both knees.

For two days after the patient was admitted to hospital the temperature was elevated one degree (Fahrenheit) at 4 p.m. but remained normal thereafter except when fever therapy was given.

The ulcers slowly became larger and deeper. The wounds made in excision of material for biopsy did not heal. The area of induration enlarged to 10 mm. back of the limbus in each eye. The patient was given 3.5 million units of penicillin, 30 gm. of streptomycin, and for four days was given therapeutic dosage of sulfadiazine in conjunction with local application of sulfathiazole and sulfacetamide, in succession or combination, without effect on the course of the disease.

When it became evident that the biopsy wounds were not healing, the ulcers were treated with a thermophore. Although this therapy stimulated some healing, it had to be discontinued because of a temporary rise in intraocular tension to 60 mm. of mercury (Schiotz).

After the patient had been under treatment for two months mild uveitis developed. It responded to foreign protein therapy with typhoid antigen, but the treatment had no effect on the scleritis. Operation to cover the ulcer in the right eye with a conjunctival flap was carried out. A specimen of diseased episcleral tissue was removed for guinea pig inoculation and the remaining episcleral tissue was cauterized with heat. A conjunctival flap was placed over

the entire ulceration and cornea of the right eye. Both eyes then began to improve. The patient was discharged from the hospital on November 1, 1949. No symptoms developed in the inoculated guinea pig, and when it was examined at the end of six weeks, no evidence of tuberculosis was noted.

A month after the patient was discharged, two firm, yellow scleral nodules which caused some discomfort appeared on the right eye, 10 mm. from the limbus. One was 3x6x1 mm. and the other 3x3x1 mm. The ulcer of the left eye was shallow and partially healed at the limbus. In January 1950, about six months after the onset of the condition, there was a recurrence of uveitis in both eyes. Reaction to a skin test at that time with 0.1 mg. of old tuberculin was again 1 plus in 48 hours. The uveitis improved and the patient was discharged after three weeks. In February the patient complained of pain in the chest and productive cough with some fever. In an x-ray film of the chest taken February 7 no evidence of active disease was noted. The patient was readmitted to the hospital in March, and an x-ray film then gave evidence of pneumonitis in the base of the right lung. The sedimentation rate was greatly accelerated. A culture was positive for Mycobacterium tuberculosis. The patient was transferred to a tuberculosis sanitarium in April. At that time both eyes were healing and the uveitis was inactive. The iris of each eye was bound down by many posterior synechiae. The scleral ulcer of the left eye which had not been covered by a flap was present but smaller. The scleral ulcer in the right eye had healed. Nodules were present in both eyes about 10 mm. off the limbus. In the right eye one nodule had healed to some extent, leaving the sclera thinned. The dark uvea could be seen through the yellow, semi-fluid center of the nodules. The patient died May 20, 1950, of pulmonary tuberculosis.

PATHOLOGY

In examination of specimens of tissue taken from the margin of an ulcer in this case of scleromalacia perforans it was noted that the conjunctival and episcleral tissue at the ulcer margin was in reality the edge of a nodule, the top of which had sloughed away.

The cellular debris in the ulcer margin consisted mainly of lymphocytes, polymorphonuclear leukocytes and plasma cells with nuclei in various stages of degeneration. The wall of the ulcer was composed of epithelioid cells infiltrated by many lymphocytes and plasma cells. Occasionally a plasma cell was seen to have undergone some colloid degeneration. In the wall of the ulcer were several giant cells having nuclear arrangement of Langerhans type. No histiocytes were observed in this section. There were fibroblasts surrounding and among the epithelioid cells but a notable lack of new vessels. The vessels near the margin of the ulcer were surrounded by small collections of lymphocytes and plasma cells. No actual thrombosis was noted in the section.

The features usually observed in examination of tissue in cases of scleromalacia perforans are (1) necrotic scleral nodules containing lymphocytes and degenerated collagen located in the anterior sclera; (2) epithelioid cells surrounding the necrotic center, often in radial arrangement; (3) giant cells of Langerhans type, but no macrophages.

DISCUSSION

Verhoeff made extensive histologic study of the lesion in the case reported by him. He described the lesion as a central mass of necrotic lymphocytes surrounded by five or six layers of radially arranged epithelioid cells. An occasional giant cell of Langerhans type was present, but there were no macrophages. Some eosinophils were present.

Prior to Verhoeff's exhaustive study, the only description of pathologic material was that it was either chronic inflammatory tissue or non-specific granulomatous tissue.

A case first reported by Kiehle in 1937[5] was described histologically in 1946.[6] The description closely paralleled that of Verhoeff, as did a case studied by Harbater in 1949.[4]

Eggers[3] reported similar microscopic observations in a case of what was termed *necroscleritis nodosa*, a name first advocated by Verhoeff[11] in 1938.

The case presented herein differed from the one first described by Van der Hoeve in that there was more diffuse episcleritis which spread downward to the sclera. In no previously reported case was there bilateral ulceration except where a nodule has been incised, and ulcers of that order usually remained indolent with little or no response to treatment. The sudden appearance of ulceration in the present case possibly represented obliterative periarteritis or endarteritis in the area involved, as that condition was frequently observed histopathologically, around the nodules.

The patient had hypertrophic arthritis but the absence of true rheumatoid arthritis in the case here reported is not distinctive. The occurrence of pulmonary tuberculosis, which was the ultimate cause of death, created a differential diagnostic problem. The eye could not be obtained for final complete pathological examination.

The similarity of the essential lesion of this disease to that of subcutaneous rheumatic nodule and to a tubercle must not be overlooked. The necrotic connective tissue and the cellular debris in the center surrounded by epithelioid cells is common to these three lesions.

The occurrence of ulcerative tuberculous scleritis or even a tuberculous process in the eye at all in the presence of active pulmonary tuberculosis is extremely uncommon. The facts that there was no response to streptomycin and that cultures and guinea pig inoculation were negative for tuberculosis were taken as presumptive evidence that these nodules and ulcerations were not primarily tuberculous. This was substantiated further by the biopsy of the ulcer margin, in which the conditions observed were not the pathologic changes associated with tuberculosis.

It is possible that the repeated use of fever therapy for the uveitis reactivated old quiescent pulmonary tuberculosis, but repeated tests and x-ray films gave no indication of pulmonary disease until the patient had been under treatment for eight months.

In several of the cases reported by other investigators cultures and animal inoculations were carried out, but in none was a tuberculous process demonstrated. Verhoeff stated that if the disease were of tuberculous origin, material from the lesion would be extremely likely to infect a guinea pig. He called attention to the fact that, although all the elements of a tubercle are present in many kinds of lesions, it is generally accepted that the cellular arrangement is the diagnostic feature. In none of the histologic material in any case was the typical eosinophilic center of epithelioid cells surrounded by lymphocytes of a typical tubercle observed.

There are more giant cells in scleromalacia perforans and not the characteristic palisading usually seen in a subcutaneous rheumatoid nodule. Possibly there is a slight alteration in the lesion because of some special reactivity of the scleral collagen. The proximity to the surface and consequent lower temperature may be of consequence. However, it is felt that the lesion is most probably a rheumatoid subcutaneous nodule in the eye.

In the tubercle, giant cells are produced in response to the presence of a fatty acid which is present in the organism. No source of this or any fatty acid is known in scleromalacia perforans at this time. Other chemical stimuli to

giant cell formation remain to be described. There may never be enough cases of scleromalacia perforans to permit as complete a study of the chemical factors as there has been in tuberculosis. Great strides have been taken in the past years in this field in other collagen disease, and inference from these studies may help answer questions about scleromalacia perforans. The response or lack of response to cortisone will certainly add to understanding of basic pathological chemical factors of the lesions. Cortisone was not available for the patient in the present case.

SUMMARY

A case is presented of scleral disease which clinically and pathologically resembled scleromalacia perforans, having scleral nodules progressing to indolent ulcers. The diagnosis was complicated by pulmonary tuberculosis. Local therapy appeared to be of value only in controlling secondary infection. Healing at the sites at which specimens for biopsy were excised from nodules was unsatisfactory; ulceration occurred and not until a conjunctival flap was placed over the wound did healing take place.

523 West Sixth Street.

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Discussion by* A. R. IRVINE, JR., M.D., *Los Angeles

In recent years there has been considerable evidence that collagenous tissues often react violently to various antigens. This so-called hypersensitive state is particularly apparent in the scleral diseases described in the foregoing presentation. In addition to its high collagen content, the sclera is comparatively avascular. These two factors are primarily responsible for the clinical and pathological characteristics of scleral granulomatous disease. In this regard I have never been impressed with the distinguishing characteristics of the various types of clinical scleritis described by the author. It appears that the classification of keratitis as brawny, sclerosing, or as scleral malacia, is dependent upon a difference in degree and location rather than a difference in type of inflammation. Chronic granulomatous disease within the sclera produces multiple small foci of necrosis because of the avascular nature of the sclera, whereas a similar process in a tissue with a good blood supply might well develop to considerable size before necrosis occurs. The scleral pathologic changes encountered in the conditions discussed by the author depend upon the peculiar hyperreactive state and the histologic nature of the sclera, and have a wide variety of etiological agents.

Since the advent of cortisone, it has become extremely important to determine the specific cause in any given instance. Whereas many cases of so-called non-specific scleritis respond well to the use of cortisone, it is becoming evident that where bacteria are present the use of that drug is contraindicated. It appears clinically and experimentally that although cortisone suppresses the inflammatory response, it does not repress the growth of bacteria. Rabbits infected with tubercle bacilli will show apparent improvement and rapid regression of inflammation when treated with cortisone only to have massive necrotic lesions develop in which large numbers of tubercle bacilli are seen after a period of time in spite of continued cortisone therapy. The same is true of experimental syphilis. I have seen two instances of spontaneous perforation of disciform keratitis after prolonged treatment with cortisone drops. In another case a patient with chronic granulomatous scleratitis and uveitis became much worse and had perforation and atrophy of the involved eye after the use of cortisone topically and systemically. It becomes apparent, therefore, that it is not sufficient to classify scleral disease on the basis of its location and pathological anatomy, but that it is necessary to continue to search for the specific etiological agents.

Perineal Myoma

MILTON Z. LONDON, M.D., *Los Angeles*

TUMORS IN OR NEAR the prostate usually present no great diagnostic problem. Occasionally there may be clinical uncertainty as to whether a mass is primarily rectal or primarily prostatic. Most enlargements or masses in this area are owing to changes within the prostate—most frequently benign hyperplasia, malignant neoplasm, prostatic cyst, or prostatic abscess. Some masses deep in the perineum may arise as periurethral abscesses, others as perianal abscesses. Other lesions which may be felt by the examining finger as a mass in the region of the prostate are cysts of the seminal vesicle or of Cowper glands. Sarcoma may originate in or adjacent to the prostate and cause unusual rectal findings.

In the case here reported an unusual lesion raised a problem in the differential diagnosis of what might be called periprostatic tumors. In a careful survey of indexes of medical literature and various textbooks of urology and pathology no mention of a similar instance of perineal myoma was found.

CASE REPORT

A 41-year-old man was first observed May 20, 1949, because of complaints of urinary frequency, urethral irritation, feeling of resistance to emptying of the bowel or bladder and feeling of fullness in the perineum for the preceding month. These symptoms were first noted in association with non-specific urethritis.

Temperature was 99.2° F. Blood pressure was 230 mm. of mercury systolic and 140 mm. diastolic. The urethral meatus was hyperemic and contained a small drop of clear mucoid material. On rectal examination the prostate felt small and of normal consistency. Immediately above the prostate on the left side was a spheroid mass about an inch in diameter. It felt cystic.

Urine in both glasses of a two-glass test was cloudy and contained shreds of blood and mucus. The pH of the urine was 5.5, the specific gravity 1.018, and albumin content 3 plus. It contained no sugar. Upon microscopic examination

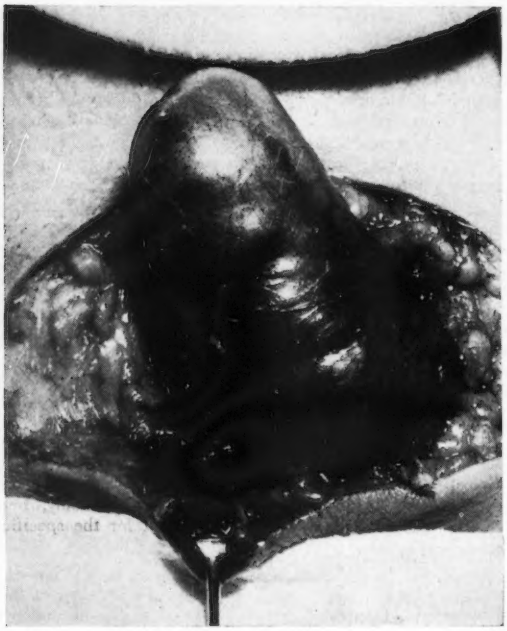

Figure 1.—Largest lobule of the mass in process of being dissected out of the perineum.

of the sediment many erythrocytes and leukocytes were noted. No bacteria were observed in Gram stained or in Ziehl-Nielsen stained smears. Pus cells were noted in a smear of material from the urethra, but no bacteria were seen in a Gram stained specimen.

The patient was treated with sulfadiazine for one week and the urethral discharge, pyuria and hematuria promptly cleared. The mass and the obstructive symptoms persisted. An intravenous urogram was made on May 28, 1949, and both kidneys were roentgenographically normal. Upon the floor of the bladder was the imprint of a large mass in the region of the prostate. A post-voiding film showed moderate retention of dye in the bladder.

Several attempts were made to aspirate material from the mass through a needle in the perineum, but no fluid was obtained. As hypertension and albuminuria persisted, consultation was advised and the consultant diagnosed "essential hypertension" of fairly advanced degree. The endogenous creatinine clearance was reduced to about two-thirds of normal, indicating definite impairment of renal function.

On September 8, 1949, the perineum was explored surgically. With the patient in the perineal lithotomy position the mass could be seen and felt bulging in the left ischiorectal fossa. The left two-thirds of a perineal prostatectomy incision was made. The most superficial lobule of the tumor was promptly exposed in the superficial fatty tissue. By careful dissection a multilobular encapsulated tumor was removed from the perineum. One lobule (Figure 1) was the mass adjacent to the prostate that had been felt previously. There was no attachment to prostatic capsule or bulbous urethra.

Pathologist's report: The specimen was an 8x7x2 cm. flabby lobulated mass of tissue, composed of confluent irregular, poorly defined lobules. Sectioned, the substance was

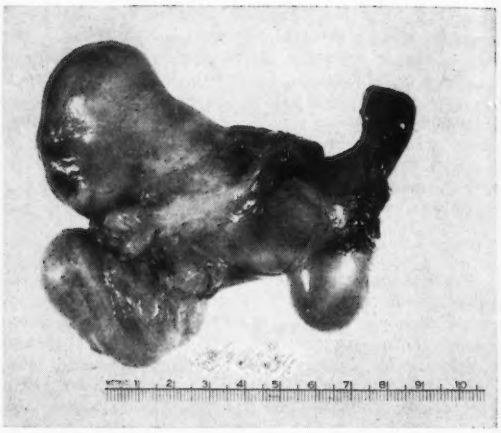

Figure 2.—Gross appearance of lobulated myoma.

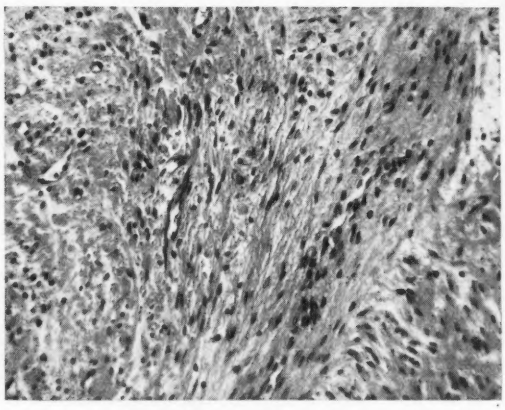

Figure 3.—Microphotograph showing uniform fibromuscular structure of the tumor.

observed to be fairly uniform, translucent, pink-gray and semi-gelatinous (Figure 2). Microscopically the specimen was observed to be a circumscribed nodule composed of fibromuscular tissue. Some of the intervening stroma was loose and fibrillary and edematous. The lesion was quite vascular (see Figure 3).

The diagnosis was: Myoma, perineum. The pathologist commented that the lesion could have originated from preformed vessels, from the prostate, or possibly from muscle near the base of the penis.

The wound healed promptly and the patient left the hospital on the fifth postoperative day. Subsequently he reported greater ease of urination and of defecation. The blood pressure was the same after the procedure as before.

SUMMARY

A case of perineal myoma is presented. Differential diagnosis and possible origin of the tumor are considered. This is believed to be the first report of an encapsulated myoma occurring in the perineum of a male.

6515 Wilshire Boulevard.

California MEDICINE

EDITORIAL

California Medicine Takes A New Look

IN THE PAST six and a half years an attempt has been made to develop the scientific side of CALIFORNIA MEDICINE so that it would be truly representative of the best of medicine in California. With the interest and cooperation of the Editorial Board and Editorial Office this has been accomplished to some extent. At the direction of the Council of the C.M.A. and beginning with this issue of January 1953, the organizational side of CALIFORNIA MEDICINE will be further developed to reflect as accurately as possible the official position and views of the California Medical Association on problems which vitally affect all aspects of medicine, and to report events and developments throughout the state and the country which bear significantly on the practice of medicine, on medical education, on medicine in government and government in medicine.

In the further development of the organizational side of this Journal, the Editor and the Editorial Board will welcome criticisms and helpful suggestions.

With this issue, consideration is given to two highly important problems facing the physicians of California. One of the most important issues of the day in the practice of medicine relates to the free choice of physicians by patients. We hold that the free choice of a physician by a patient is essential for the best medical care and for an adequate physician-patient relationship. To whatever extent this principle is compromised, there is likely to be proportional deterioration in medical care and, all too often, an increase in the cost of that care. Closed panel forms of practice do not permit free choice of physician and in other ways tend to cause deterioration of the best in medical care. A more complete consideration of this most important problem is noted in the editorial entitled "A Defense Against Socialized Medicine"?

So that many physicians in California may become acquainted at first hand with the very significant report of an eighteen months' study by a special committee to consider the desires of the California Medical Association in relation to C.P.S. and voluntary health insurance, there is published in this issue the full report of the Bailey Committee, given to the House of Delegates at its Interim Session in December 1952. This thought-provoking report should be discussed fully in every county medical society throughout the state, so that in May 1953, when the House of Delegates reconvenes in Los Angeles, the members of the House will be well informed of the views of their constituents and prepared to take appropriate action.

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For information on preparation of manuscript, see advertising page 2

"A Defense Against Socialized Medicine"?

A RECENT EDITORIAL in the *New England Journal of Medicine* cites closed panel medical plans in general, and the "Permanente idea" in particular, as "worthy of careful study by physicians throughout the country as one type of program that may not only erect further defenses against the encroachment of socialized medicine, but actually provide more and better medical service, at lower cost, and at the same time maintain the dignity of both doctor and patient."

In California, we have long carried out the "careful study" of closed panel plans which the editorialist recommends. We have had the advantage of direct observation, so that our conclusions need not be based wholly upon a report of the medical director of such a plan, which the *New England Journal* admits "might be interpreted as being tinged with enthusiasm and self-interest . . ."

Our study shows closed-panel plans destroy the doctor-patient relationship. This destruction begins with the plan salesman, who must convince the prospective buyer it is to his advantage to break his relations with his personal physician. This is necessary because these plans offer no provision for indemnification of the patient who prefers his own doctor to the plan doctors. Then, having become a member of the plan, the patient finds many barriers to the establishment of the desired personal physician-patient relationship. We have just received a letter from a patient which is only a variation on the familiar theme. She went to the plan doctor in her area, who sent her to the nearest Permanente plant (Oakland) to complete spontaneous abortion. There her treatment was handled by three successive doctors, none of whom she saw more than once. So, she will drop the plan, she says, and return to her personal physician, who will see her through any illness.

Another destroyer of the doctor-patient relationship is the turn-over of Permanente doctors. There are at least 35 former Permanente doctors now in private practice in the East Bay area alone. What percentage went elsewhere, we do not know. This parade of doctors into and out of a closed-panel plan in itself precludes sufficient continuity to establish and maintain the kind of relationship between doctor and patient necessary to the total medical care needs of the whole patient.

We find also that closed panel plans rob the patient of his freedom. He may not dismiss his plan physician and select another of his choice outside the plan without loss of protection for which he has paid. Under the Permanente plan, for the same reason, he cannot change hospitals. The subscriber contracts today for whatever quality of service may be available from the plan at an indeterminate future date—the date of his future illness. And he is "stuck" with whatever quality of service is then given to him. The patient thus becomes the captive of the plan. One California closed-panel plan recently changed ownership; its patients were "bought and sold." The subscriber who is dissatisfied with the service, or who at the time he is ill would feel confidence only in a physician who is not a captive of the plan, does have a choice. He may take the unsatisfactory service, or he may write off his health plan dues as an ill-advised investment and pay the total cost of his care to the doctor of his choice. Many choose the latter.

A dangerous element in closed panel plans will be immediately obvious to every student of the force of incentive in human relations. This is a particularly important factor when incentive concerns a contract for a service that is so difficult of evaluation and measurement as medical care.

The *Permanente Foundation Medical Bulletin*, cited by the New England editorialist, talks about incentive thus: ". . . This results in a reversal of the usual economics of medicine. The well person becomes an asset to the hospital and doctor—the sick person a liability, thus heralding the preventive medicine of the future." The preventive medicine of Permanente so far is truly for the future; we have found no evidence of present achievement. But we agree that the closed-panel plan makes the sick person a liability to both hospital and doctor. The incentive, then, is to withhold treatment, to use short cuts, or to cheapen it, which is the reverse of the incentive of the doctor in private practice.

The only kind of medical economics that guarantees protection of the patient's interests is that which gives incentive to the doctor to prescribe and treat as much as the patient needs. Few people — even doctors — forever violate their own interests.

And now, specifically as to Permanente. Who and what *is* Permanente? In California, when we have difficulty with Permanente, we start with the doctor or doctors then acting as medical directors and end up talking to Mr. Henry Kaiser. We have no technical proof that Permanente is the practice of medicine by a layman. But we inevitably end up talking to—or, more accurately, being talked to and often threatened by—Mr. Kaiser. Our medically trained minds cannot follow Permanente's intricate intercorporate entanglements, rental arrangements, partnerships, interorganizational contracts and pooled personnel and purchasing arrangements. But we

know that what Mr. Kaiser says will happen in Permanente usually happens.

Here, then, in our opinion, is the pattern for lay practice, control and direction of a profession. We need not argue the public interest factors in this condition. They have long since been decided and repeatedly reaffirmed by the courts. How many profit-minded laymen will see in the "Permanente idea" the opportunity to "reverse the usual economics of medicine" for themselves? And what will they do with it? Whom will they exploit? And to whom will they be answerable?

Typical of the mechanistic "efficiency," of the unprofessional approach of Permanente to medicine, is its solicitation of patients. We assume it is unnecessary to quote or interpret the Principles of Medical Ethics of the American Medical Association to our readers. Patients in every group sold by Permanente are solicited, with the full knowledge of "Permanente" but not with the full knowledge of all of the *doctors* of Permanente. Many members of these employed groups are currently under the treatment of other doctors. Our studies of Permanente reveal that either the ethical prohibition of solicitation of patients by any doctor is wrong, or all Permanente doctors are unprofessional and unethical. Doctors outside Permanente may not solicit patients; Permanente doctors solicit their patients.

Much is made of the financial success of Permanente. Captive doctors, seeing and treating many patients, is one reason. Interns and residents treat some—how many we do not know. Another reason for financial success is that many subscribers who enroll do so reluctantly, as minority members of employed groups. These persons continue to go to their private physicians, keeping Permanente insurance in the background for catastrophes. It is difficult to find a private physician in the East Bay "stronghold" of Permanente who does not have Permanente plan members who continue — even for major operations—with their personal physicians. Each such visit, each such treatment paid for by the patient, is a contribution to Permanente's spectacular financial success.

If the values of the art and science of medicine can be measured by an industrialist's standards of production and efficiency and profit, Permanente is an unqualified success. But medicine has other standards.

The Boston editorialist believes that closed panel plans may provide "more and better medical care." It has not yet been produced by these plans. "Lower cost"? Yes, in premium. "Maintain the dignity of doctor and patient"? Former Permanente doctors have regained their dignity in private practice and lose no opportunity to dispute that claim.

As to the patient's dignity: the closed-panel plan tells him he can't select his own doctor. Permanente can do it better, despite its doctor turn-over record. The patient is assigned to a doctor, is told by the plan what treatment he gets, by whom and where. He is *not* free to exercise his own judgment and choice. Can this maintain his dignity?

Our confidence in the good judgment of the American people is such that we are not deeply concerned about the future of closed-panel plans. The "Permanente idea" is *not* new. The history of nearly every medical society will reveal the same problem under the name of "Lodge practice," with inevitably the same result as we predict for the closed-panel plan. The people will make the final determination. Our studies show they want their personal physicians, whose incentive is to serve them and not some third party—union leader, government agency, lodge master or industrialist.

So, we too would join the *New England Journal of Medicine* in counseling study of closed-panel plans. The more thinking and study, the more experience doctors and patients have with closed-panel plans, the more each will realize that it is pointless to "erect further defenses against the encroachment of socialized medicine" if those defenses consist mainly of instituting the worst dangers of socialized medicine.

New Approach

MOST SIGNIFICANT development emerging from the 1952 Interim Session of the C.M.A. House of Delegates was the proposed new approach to the problem of providing insurance against the costs of medical and hospital care. The C.P.S. Study Committee, crystallizing its intense research of the past eighteen months, offered a plan which is startling in some aspects but which basically appears as a new and sound appraisal in this still experimental field.

The committee report proposes (a) that indemnity insurance be utilized as the carrying agent, (b) that co-insurance govern the underwriting procedure, with the policyholder accepting his legitimate share of the risk, (c) that "average fees" be worked out, successively, by individual physicians, by county or regional areas, and by the state as a whole, and (d) that deviations upward from accepted "average fees" be undertaken only with the knowledge and consent of the patient. Failure to accomplish the last of these proposals would be *prima facie* cause for the patient to seek the counsel and aid of the

professional conduct committee of the county medical society.

While none of the above proposals is new in itself, the combination under this suggested program represents a new concept in the search to provide top-flight medical and hospital care under conditions and at fees which are acceptable to, and may be afforded by, the general public.

In the next few months the county medical societies will ask themselves and their members whether or not they wish to accept this far-reaching proposal. Most knotty problem apparent in the coming deliberations will be the establishment of "average fees" by individual physicians and by their county societies. Upon this branch of the proposal hangs a large measure of the potential success of the entire program.

The entire text of the study committee's report appears elsewhere in this issue of CALIFORNIA MEDICINE. Every member should read this document carefully, repeating the process as needed to assure a complete understanding of the philosophy developed after months of study, testimony, discussion and deliberation. Here is proposed a new approach to the ever-growing problem of health insurance. The considered opinions of all county medical societies will be vital in determining whether or not this plan offers the ideal path for medicine to take in leading the way to a great public service.

Increase in Cancer Incidence

FOLLOWING COMPLETION of a cancer survey in the Birmingham, Alabama, area in 1948, National Cancer Institute reports a 71 per cent increase in incidence and a 50 per cent increase in total cases treated since the last survey there in 1938.

Dr. John R. Heller, institute director, attributes the increases partly to better reporting by physicians, improved diagnostic and case-finding methods, and aging of the population. ". . . The survey shows that more cancer patients received hospital care in 1948 than in 1938, due in part to the increase in hospital facilities in Birmingham," he said.

The survey, eighth in a series by the Institute, was carried out with help from the Jefferson County Medical Society, the Jefferson County Hospital and Birmingham, Jefferson County and State Health Departments. — *From the A.M.A. Capitol Clinic.*

California MEDICAL ASSOCIATION

NOTICES & REPORTS

C.M.A.-C.P.S. Study Committee Report

The following report was made December 6, 1952, by a committee appointed by the Council of the California Medical Association in accordance with a resolution passed by the House of Delegates of California Physicians' Service at its 1951 annual meeting. The purpose of the committee, as stated in the resolution, was "to ascertain the expectations of the medical profession of California in regard to C.P.S."; and the function of the committee, as set forth in the resolution, was "to make a careful study of C.P.S. as related to the operations of private insurance companies and other prepaid medical care groups, and to determine the future role and purpose of California Physicians' Service in the whole field of voluntary prepaid medicine."

The membership of the committee appointed by the Council is as follows: Wilbur Bailey, chairman, Los Angeles; James B. Graeser, vice-chairman, Oakland; Paul D. Foster, vice-chairman, Los Angeles; Alson R. Kilgore, San Francisco; Dave F. Dozier, Sacramento; Francis E. West, San Diego; J. M. de los Reyes, Los Angeles; Harold P. Tompkins, Los Angeles; Donald A. Carson, San Francisco; Gary Campbell, Santa Barbara; Henry Randel, Fresno; F. E. Clough, San Bernardino; Thomas Farthing, San Mateo; Leslie B. Magoon, San Jose; Edward C. Rosenow, Jr., Pasadena.

Mr. Rollen Waterson, executive secretary of the Alameda-Contra Costa Medical Association, served as executive secretary of the committee.

THE FIRST PORTION of our report constitutes a follow-up on the progress which has been made on the five specific recommendations in our interim report submitted to this House at the meeting held April 27-30, 1952. We shall then present further recommendations as determined during the last 18 months in some 50,000 doctor-hours of work by the 15-man committee appointed by the California Medical Association to study California Physicians' Service. Lastly, we shall present a summary.

1. *Multiplicity of Contracts.* C.P.S. now has ten basic contracts which constitute 96 per cent of those which are written. The other 32 types of contract constitute only 4 per cent. Progress is being made toward further simplification, for at the present time a collection of the various contracts is almost as thick as a telephone book. Contracts tailor-made to fit the wishes of small groups are not only confusing but are actuarially dangerous. It is hoped they will be avoided in the future.

2. *Method of Payment.* It was recommended by this committee that the previous policy be reversed, and that the patient should in the future be told how much was being paid the doctor by C.P.S., either by the method of a double-signature check such as is used by Blue Cross in its more than 500,000 accounts in Southern California, or by some other means. C.P.S. has started such a system on a very small scale in a few small communities. To date the experiment is successful.

3. *Defective Liaison Between C.P.S. and C.M.A.* The Council has up to this time appointed three of its members to the Board of Trustees of C.P.S. by way of improving the liaison between the two groups.

4. *Imperfect Communication.* More personalized methods of communicating with the doctor have been established.

5. *Blue Cross-Blue Shield Relations.* A recommendation was made most emphatically that the Council of the C.M.A. undertake to negotiate with the Boards

of Trustees of Blue Cross plans and the California Hospital Association to achieve cooperation between these plans. Obviously, the catalyst in such a situation should be the C.M.A. Such recommendations were made by your committee to the House of Delegates and later to the Council. However, no such meetings have as yet been arranged by the C.M.A.

It has been further called to the attention of our committee that it is very necessary for outstanding public-spirited medical citizens to become future officers of C.P.S. The best cannot be expected from this $20,000,000 corporation if its trustees are selected in a hurried conference just before the delegates convene. Nor should newly-elected trustees be expected immediately after their election to select a president.

As a final phase of this review on progress made to date on our recommendations, the committee believes that much has been accomplished but there is still much to do to eliminate that great bugaboo of all Blue Shield plans—*overuse*. Disciplinary action has been taken by various county medical societies.

FINAL REPORT

This is the final report of your C.M.A.-C.P.S. Study Committee, appointed eighteen months ago to "ascertain the expectations of the medical profession of California in regard to California Physicians' Service in the whole field of voluntary prepaid medicine," to quote the resolution by which your committee was created.

California Physicians' Service was incorporated in 1939 by a group of physicians—members of the California Medical Association—for the purpose of creating a voluntary, prepaid medical care plan to be sponsored by the medical profession of California.

The men who organized C.P.S. wrote into its Articles of Incorporation this statement: "We . . . do hereby declare that the duties and obligations of the [medical] profession are not only leadership in the maintenance of high standards of medical service, but also in the means of distribution of that service so that all who need it may receive it."

That statement was true then; it is doubly true today. As the years have passed and the rapid alterations of the national economic climate created by the war and its sequel of confusion have been reflected in the economics of medicine, new problems have been piled upon the old. Both the rich and the poor have become fewer. Today, a person nominally in a low income group may, from the point of view of protection against expenses of illness, actually be in a higher income category because of fringe benefits included in his union contract. Many people and groups, besides doctors and patients, have developed a burning interest in health insurance.

Caught in this confusing cross current of vigorous, undirected forces is the physician. But he cannot give up, he cannot withdraw, because he still knows deep down that it is he, the physician, who must face up to the responsibility of diverting these cross currents into one powerful stream whose single direction will be toward the greatest good of the people of America.

Your committee has examined criticisms of California Physicians' Service by both physicians and laymen in its effort to discover the reasons for failure of physician acceptance and the causes of lay dissatisfaction. We have consulted representatives of every interested group, and we have employed experts in the fields of insurance and of consumer research. We confess that we have many times made up our collective mind, only to have new evidence or deeper study change it for us. We have allowed ourselves, too, the luxury of inconsistency, as comparison of our interim report with this final report will demonstrate.

Our experience thus emphasizes that no final answer to the many problems of health insurance can be written today. We have learned above all else that no committee such as ours, no national or even international expert, no group of insurance underwriters and, least of all, no covey of government bureaucrats, can do more than chart a tentative course of action, leaving always ample room for shifts of policy as experience proves a given course to be in error.

Nevertheless, and at this present moment, we believe that any of the ten thousand members of the California Medical Association who had been subjected to the same long, laborious education as have we, would have come to share the convictions we present in this report.

We submit this report with profound humility, and with a deep realization of its limitations.

The first step in a rational attack upon the problem of health insurance must be the reduction of its complexities as near as possible to their fundamentals. Of these, the most basic seems to us to be a definition of exactly what we mean by the term "health insurance."

Your committee defines health insurance as the application of the insurance method of group assumption of an individual financial risk to the costs of private medical care. It is important to realize that it is *not* the purpose of health insurance *as such* to reduce the costs of illness, to change the distribution nor to improve the quality of medical care, to alter the pattern of private medical practice, nor to be an instrument for social change (with all the connotations that term implies).

There stems from our definition the obvious fact that health insurance concerns two separate and very

different fields of human endeavor: The business of insurance and the profession of medicine. This division leads us to a restatement of our problem, thus: What are the basic principles of insurance as a business, and what are the basic elements of medicine as a profession, both of whose tenets must be considered if the techniques of one are to be applied to the other?

Principles of Insurance

The first is that group assumption of an individual financial risk is economic only if the possible size of individual loss be large, and the individual expectancy of loss occurrence be small. To quote Linder, our actuarial consultant: "*Insurance is at its best when it protects against the large loss which is unlikely to happen, and at its worst when it protects against the small loss which is likely to happen.*" It is obvious that group payment of small losses which are almost certain to occur to most of the members simply increases the cost of medical care by the amount of administrative expense and thus *rather than protecting against loss, increases it.*

The second principle, that insurance must act only *to mitigate the loss* and not to reward the loser, is one whose obvious basis is the human element.

The third principle is that the primary value for which the insurance premium dollar is paid is protection. Failure to sustain a loss against which insurance protects should be a matter for self-congratulation and not grounds for the policyholder to feel that he has not received something for which he has paid.

Our fourth principle is that *insurance can be written only against a determinable risk.* Loss expectancy is a function of two factors: The frequency of occurrence of loss and the average amount of each loss. Without a statistically determinable figure for each, underwriting becomes guesswork and the accurate determination of premium rates is impossible.

So much for the principles of insurance.

Elements of Medical Practice

Our second question was: What are those elements of medical practice upon which will fall the impact of any changes in medical economics?

The first such element is the greatly increased costs of modern medical and hospital care. The financial burden of serious illness can be enormous even on those in comfortable circumstances, and can be catastrophic on those of modest means.

The second element of medicine which is germane to our problem is that the occurrence of *major illness is relatively infrequent* and wholly unpredictable to the individual, but the frequency of such illnesses in a group large enough to be statistically significant is relatively constant.

The third element of the economics of medicine which bears on the application of insurance to health costs is the wide variation in costs of care for any given type of illness. Besides the variation resulting from the fact that medicine is a biologic and therefore an inexact science, there are those other variations due to great differences in patient demand for service and those which result from the varying opinion of physicians as to the necessary amount and the monetary value of their services.

The fourth professional element requiring consideration is a trend rather than a fully established and accepted practice, and represents a change in the traditional economics of medicine. That element is the trend toward uniform fees; a trend which consists of three components: First, the trend toward a fairly uniform scale of fees on a community basis; second, the trend toward fairly uniform fees within each specialty of medicine, irrespective of geographic considerations; and third, the trend toward a uniform, individual schedule of fees for each physician which, while based to some extent on the general level of fees in his community and the average schedule of his specialty, varies with his prestige, experience, skill and with patient-demand for his services.

It is important to note, however, that this trend toward uniform fees is only a modification and not a nullification of the traditional practice of determining fees on the basis of the patient's ability to pay, in that this uniform fee scale is used as a base from which deviation is frequent as the patient's economic status dictates. Further, this deviation more often is in the direction of reduction where need demands and less often is in the direction of increase for the well-off patient. We think that most of you, if you will examine your own practices, will confirm these observations.

The fifth element of medicine affecting our problem is at the same time the most difficult to describe and the one whose protection and preservation is to us most vitally important. That element is the personal relationship between patient and physician which follows from the fact that medicine is an art as well as a science, and a profession rather than a business. This relationship is the foundation for the practice of good medicine, and is the virtue of private medical practice to which both patient and physician cling.

To the patient, around this element revolves his right to free choice of his doctor, and his desire to retain full freedom of action in caring for his health as in caring for all his other material needs. The great majority of our citizens still believe in the benefits conferred by the free-enterprise system, and in the virtues of individual freedom and the right of self-determination. And they want no compromise with these principles in any field of endeavor, medicine included. Further, the patient knows that if a

third party intrude into the traditional two-party relationship between himself and his physician on an economic plane, there will inevitably result an equal intrusion on the professional plane.

To the physician, too, around this element of an exclusive bipartite relationship between himself and his patient revolves the doctor's desire to remain an independent individual whose economic as well as professional decisions are his alone to make. But, more than that, it concerns his certain knowledge that his effectiveness as a physician depends on maintaining inviolate an intimate two-party relationship of doctor to patient.

For purposes of convenience in the following discussion, this element will be identified as patient-physician freedom but, when that term is hereafter used, its full connotations must be remembered.

These, then, are the basic principles of insurance as a business and the important elements of medicine as a profession. Our next step is to examine the application of one to the other.

Insurance Principles Applied to Medical Economics

Our first insurance principle was that group assumption of an individual financial risk is economic only if the possible size of individual loss be large, but the individual expectancy of loss occurrence be small. Our applicable elements of medicine were first, that the financial impact of serious illness can be enormous, and second, that serious illness is infrequent and unpredictable to the individual but is a relative constant in the group. One inescapable fact seems to us to derive from these premises—that only the costs of serious illness constitute an insurable risk.

While accurate definition is difficult and many variables intrude, to the physician the basic differences are those of comparative frequency and relative expense. To any given individual, major illness is infrequent and expensive; minor illness is frequent, and its legitimate expense per disability is low. But the most important difference between major and minor illness is the element of patient control of costs. A person seldom debates the need for medical care for a fracture, for perforation of a peptic ulcer or for coronary occlusion. But whether or not he seeks a penicillin shot for his coryza will depend on his own estimate of probable benefit measured against cost and inconvenience. We are not belittling the need for medical care of many minor ailments; we are simply urging that the reasonable person uses some degree of discrimination in deciding when he needs a physician's services, and the volume of medical care rendered for minor illness will depend to a great degree on this element of patient decision. Since that decision involves the measuring of cost against benefit, any lessening of costs will increase the demand for benefit.

Our first conclusion, then, must be that the COSTS OF SERIOUS ILLNESS *are susceptible to the valid application of the insurance method, but the* COSTS OF MINOR ILLNESS *do not so qualify.*

Our second principle, that insurance must act only to mitigate the loss, *not to reward the loser,* we already have said should be self-evident. But our third medical element was that medical costs varied widely because of differences in patient demand for service and variations in the opinions of physicians as to the necessary amount of care and its monetary value. Partly because of this element, and partly because human nature is what it is, two kinds of abuses of existing health insurance which contravene this principle of not rewarding the loser are of more than occasional occurrence. The first is typified by that patient whose insurance policy pays him more as an indemnity for a medical service than his physician charges, and by that other patient, who, by a combination of insurance policies and state disability benefits, is able to earn as much by occupying a hospital bed as by working at his job. The second is typified by the patient the generous provisions of whose policy invite unnecessary service.

The only effective brake against these inflationary charges and the only way to avoid "rewarding the loser" is the practical application of the principle of patient participation in his costs. This sharing of costs by insured and insuror has a name — co-insurance.

Our second conclusion, then, is that the diversion of the premium dollar to pay claims for unnecessary service can best be prevented by applying the principle of co-insurance to health insurance coverage.

Our third principle was that the primary value for which the insurance premium dollar is paid is protection. A frequent violation of this principle which is too often unchallenged is the concept of insurance as a budgeting device. To budget an expense means to pay a fixed sum in small installments, for which exact monetary value is received in return. The lucky insurance policyholder will, however, have no monetary return for his premium, and insurance cannot therefore correctly be considered a budgetary mechanism.

A similar and even more serious misconception of the primary value of insurance as protection is the increasing trend toward the granting of health insurance coverage as a fringe benefit in lieu of a wage raise, resulting in the almost unanimous reaction of the worker that to receive this sort of pay raise, *he must somehow collect on his health insurance.* The current demand of labor for full-coverage health

insurance is to a great degree based on this feeling that *health insurance has no value unless services be received thereunder.*

Our third conclusion, therefore, is that the HEALTH INSURANCE POLICYHOLDER *must somehow be convinced that he* WINS RATHER THAN LOSES WHEN HE FAILS TO SUSTAIN A LOSS *against which his health insurance protects him.*

Our fourth principle was that insurance can be written only against a determinable risk. We have already pointed out that the advance determination of probable losses requires two figures: The expected frequency of loss occurrence and the average size of each expected loss. The limits of actuarial accuracy will be set by the predictability of these two values.

We have already agreed that the factor of incidence is sufficiently constant to be possible of accurate, advance determination. At first glance, it would seem that experience also should furnish a reliable average unit cost which would be sufficiently accurate for the actuary. For many forms of casualty coverage that may be true, but observe conditions as they exist in health insurance, necessarily modified as they are by the elements of medicine we have described. We have pointed out the effects on medical costs of the variables of patient demand and of physician opinion, and we have emphasized the virtues of physician-patient freedom. These elements, reflecting not only the tangibles of time, effort and skill, but the intangibles of personal opinion and emotion, can act only to set the extremes of unit costs literally from zero to infinity. Further, even though it be his habit in private practice to accept different fees from different patients, the physician will not accept less from an insurance company for his services than is paid his colleague across the hall. Nor will the banker pay ten times the premium for his health insurance that the janitor pays on the grounds that the banker's physician will charge him ten times as much. Thus, in practice, the use of the average size of each loss as the theoretical unit cost of any given type of illness becomes impossible, and the fixing of an actual unit cost becomes necessary. In medicine, this means just one unpleasant thing—a fee schedule.

Our fourth conclusion, then, must be that for the costs of health care to be a determinable risk and thus susceptible to the application of the insurance method, the unit costs of medical care must be set by a fee schedule.

We have now come to the point where we can see very clearly the basic dilemma of health insurance —the incompatibility of the insurance requirement for fixed unit costs with preservation of the vital medical element of patient-physician freedom. Certain and adequate protection against the costs of a major illness can be given only if the costs of that illness are set by a fee schedule, but the application of any fee schedule to the private practice of medicine is accomplished only by the intrusion into the physician-patient relationship of a third party, the insuror. Neither condition, therefore, can be met except at the sacrifice of the other.

Let us examine the conditions of our dilemma in terms of existing health insurance plans. There are two basic types of health insurance; service plans and indemnity plans. For you, these terms need no definition. There are many differences between them both in principle and in practice, but the really basic difference between them is the comparative weight each gives to the two conditions of our dilemma. Service plans, obviously, provide certainty of patient protection at a total sacrifice of patient-physician freedom. Indemnity plans, on the other hand, sacrifice certainty of protection in an effort to maintain patient-physician freedom. Thus, on the scale measuring these conditions, each plan is at the opposite pole to the other.

But, your committee asked, must we choose between black and white? Or may there be, instead, a gray zone somewhere in between these opposite poles within which a compromise might be obtained. That such a compromise might not be a vain hope seemed possible to us, if only on the grounds of an axiom that cannot be too often stated: That the best interest of both physician and patient will be fully served only if each gives full weight to the best interest of the other. That axiom, applied to the problem of health insurance, can only mean that it is to the interest of the physician that health insurance provide adequate, dependable coverage for his patient; and it is to the interest of the patient to maintain a free, unregimented medical profession with whose members his relationship remains on the same personal, two-party basis that it always has.

The defect of service-type health insurance was its sacrifice of patient-physician freedom; its virtue was certainty of beneficiary protection. Both the defect and the virtue result from the application of the principle of a fixed, compulsory fee schedule. It seemed to us that this element of compulsion is not capable of modification. There is no such thing as a degree of compulsion—it is all or none. As confirmation of this opinion, one may note that, whenever it has seemed wise or necessary to modify the service principle in a C.P.S. contract, the solution always has been to substitute for it the indemnity principle. We conclude, therefore, that no modification of service-type insurance to lessen compulsion is possible.

Now, let us approach the dilemma from the opposite pole and ask: Is there any possible modification of the indemnity-type plan which will gain certainty of patient protection without sacrificing patient-physician freedom? That there might be seemed to

us possible for several reasons, the most important of which, in our opinion, are:

First, many current indemnity plans carry a schedule whose level bears very little relationship to the usual fee for any given service.

Second, many current indemnity contracts have been slanted toward too much protection for minor illness and too little protection against costs of major illness; in other words, they ignore our criteria for insurability.

Third, and by far the most important, indemnity plans have so far been entirely a project of commercial insurance carriers without the advantages of cooperation, collaboration and assistance from the medical profession.

Our immediate problem then, is somehow to modify the indemnity principle to gain certainty of beneficiary protection without losing its virtue of patient-physician freedom—indemnity plan insurance by itself provides neither certainty nor adequacy of protection in that its indemnities may bear no relationship to the actual costs of an illness. To obtain certainty and adequacy of loss coverage, the total costs of an illness must be capable of advance determination, and that seems to bring us full circle again to the necessity for a compulsory fee schedule.

But, before we accept that as the apparent final conclusion and as defeat in our search for a compromise, let us go back to our discussion of the elements of medicine. We said there that there is a definite trend toward a uniform fee schedule, for each individual physician. At least theoretically it should follow that, if this physician adhered to his own schedule, it would be possible to write an indemnity policy against this schedule which would give real certainty and full adequacy of protection to the patients of that physician.

Now, extend this hypothetical situation to include those physicians in the same community whose standing is such that their individual fee schedules are very nearly alike. Given again that each of these physicians adhered to his own schedule, it would now be possible for the patient to choose freely between any of them and, with the same indemnity policy he again would have certainty and adequacy of health insurance protection.

If this group of physicians we describe above as having a fair uniformity of individual fee schedules constituted the majority of physicians in the community, we might fairly call them the "average" physicians, and their scale of fees would constitute the "average" fee schedule. And this "average" fee schedule would be a realistic base for the devising of an indemnity schedule which would give both certain and adequate protection against the costs of professional care rendered by these "average" physicians. If on the other hand, a patient sought care from a physician whose individual fee schedule was above the average of the community, SO LONG AS THIS FACT OF THE HIGHER SCHEDULE WAS KNOWN TO THE PATIENT, the patient would still have certainty of protection in that he would know exactly how much his costs would be increased, and he would knowingly and willingly be accepting a lower degree of protection from his health insurance. THIS IS EXACTLY THE SITUATION WHICH HOLDS IN PRIVATE MEDICINE, when the patient who seeks the specialist or the physician of unusual attainments expects to pay accordingly and is, in fact, disappointed if he is not asked to do so. The only new factor we have added in order to attain certainty and adequacy of protection is the existence for each physician of an individual fee schedule whose general level, at least, is known to the patient BEFORE he seeks service.

By thus confirming and perhaps extending what already is a strongly set trend, we believe a reasonable compromise solution to the dilemma of health insurance is possible. To make it work, each physician will voluntarily have to limit his own freedom to the extent of accepting the principle of individual uniformity of fees. And the majority of physicians in a community must devise a community fee schedule whose level can fairly be described as the average fee charged the average patient by the average doctor in that area. If, to these devices of individual and community fee schedules be applied an indemnity-type plan of health insurance, your committee believes that adequacy and certainty of beneficiary protection can be attained with only minor limitations of patient-physician freedom. This, then, is the final conclusion of your study committee: That, if it be written against a realistic fee schedule, *if it provide coverage only for those costs of health care which are insurable, and* IF IT BE GIVEN ACTIVE COOPERATION AND SUPPORT BY THE MEDICAL PROFESSION, indemnity-type health insurance can be made a good answer to the problem of health insurance.

The first two of these conditions have already adequately been discussed, but the third "if" needs amplification. What exactly do we mean when we say "if it be given active cooperation and support by the medical profession"? We mean:

First, that having accepted health insurance as a social necessity, having agreed that good health insurance can be written only against determinable costs, and having decided that the only method of fixing determinable costs without drastic limitation of patient-physician freedom is to adopt the principle of uniformity of individual fees, each member of the medical profession must be persuaded that it is to his own best interest to adhere to that principle.

Second, that each individual physician must accept the corollary of that principle that departure

from his individual fee schedule is justified only on the basis of prior agreement with his patient.

Third, that the medical profession must agree that there can be such a thing as a realistic uniform community fee schedule whose basis is the fee charged the average patient by the average doctor, and must set up machinery to devise and periodically revise such a schedule.

Fourth, that physicians must agree that, for this uniformity of both individual and community fee schedules to accomplish its purpose, both the fact of their existence and their general level must be known to the patient, and doctors must take active steps to disseminate this information.

Fifth, that the medical profession must agree that the fee charged the patient will not be altered on the basis of the existence or degree of any insurance protection the patient may have.

Sixth, that the medical profession must extend to the field of medical economics what now is accepted in the field of medical ethics, that the profession has both the right and the duty to restrain the individual from committing acts injurious to the group as a whole.

Seventh, that the acceptance by the medical profession of the existence of this right and duty carries with it the responsibility of the exercise of the power necessary to protect this right and perform this duty, and the fulfillment of this responsibility will require that the profession create machinery for investigation, prosecution and discipline of those of its members who violate economic as well as professional ethics.

May we hope that this discussion of the principles on which our conclusions and conditions are based has convinced you, as it has us, that their application can result in a kind of health insurance plan which will retain the time-tested virtues of private medical practice and still fulfill the social need for certain and adequate protection against the heavy costs of serious illness.

To achieve clarity of understanding and to promote accuracy in debate we should like, at this point, to propose and define two new terms. The first is a name for our plan as a whole—we should like to call it the "average-fee plan." We recognize that our plan is, in essence, only a combination of an existing kind of health insurance with the application and extension of an already existing economic trend in medicine. We believe, however, that it is enough of an innovation to merit a name of its own, and the term we propose—the average-fee plan—seems to us to be most descriptive. The second term is a new name for the kind of fee schedules upon whose formulation the average-fee plan depends. To us, the term "fee schedule" savors too strongly of the element of compulsory acceptance, and the essence of the average-fee plan is its avoidance of compulsive uniformity. The term "fee schedule," too, seems to us to carry the implication of fees set from above rather than our procedure of beginning with the individual and working up to the top echelon from below. We envision first the individual setting his own fees, then the county formulating a schedule based on the average of these individual scales and finally the state devising a schedule which is a composite of county schedules. For these kinds of schedule, we propose the term "fee lists," and we shall hereafter use that term to differentiate a fee schedule used in this manner from schedules otherwise applied.

RECOMMENDATIONS

We are now ready to specify the steps which we believe best will apply our conclusions. Our recommendations are divided into those whose implementation is a function of the medical profession, either as individuals or as it is organized in county medical societies and the California Medical Association, and those which concern California Physicians' Service.

First, our recommendations for steps which the medical profession should take:

1. Each individual physician shall be urged to accept the principle of individual uniformity of fees, and to formulate an individual fee list to which, in the absence of agreement with his patient to do otherwise, he will adhere.

2. Each component county medical society of the California Medical Association or its branches shall be urged to formulate, and regularly revise, a fee list whose basis shall be the average fee charged the average patient by the average physician in its county.

3. The California Medical Association shall formulate a state fee list, which shall be a composite of county lists, and which may be adopted by any county as its list in lieu of a locally determined one. The purpose of county and state fee lists shall be to serve as guides to insurors in formulating realistic indemnity schedules.

4. The California Medical Association shall establish machinery on a statewide or regional basis to handle fee complaints, which machinery shall be available to all patients whether or not they hold health insurance and, if they do, irrespective of the identity of the insuror.

5. The measure of the legitimacy of a fee complaint shall be: Whether or not the fee is consistent with the individual fee list of the physician concerned; and, if the fee charged *is* a departure from the physician's fee list, whether or not there had been prior agreement to this departure.

6. The fee complaint machinery shall include a

mechanism for enforcement of decisions, which mechanism specifically shall include the provision of expert testimony by the fee complaint committee in any litigation to force payment of a fee upon whose legitimacy the committee has ruled.

7. The California Medical Association and its component county medical societies shall initiate and maintain a continuous program of public education covering the following general points:

(*a*) The fairness of hospital costs and medical fees.

(*b*) The mirage of full-coverage health insurance; why it is that the individual will pay less for care of minor illness if he pays his doctor direct rather than through an insurance company; and why co-insurance is an essential part of good health insurance.

(*c*) The protection against the cost of serious illness which good indemnity-type health insurance can give, and the degree to which this type of health insurance protects normal, two-party relationships between the patient and his doctor.

(*d*) The fact that most physicians have an individual scale of fees upon which their charges for professional services are based. Information about this fee list is a legitimate query to be put in advance of accepting service.

(*e*) The existence of fee complaint machinery in California, and the procedure of appeal in cases of fees believed to be unreasonable.

(*f*) That, irrespective of the existence of individual fee lists, the medical profession adheres to its centuries-old responsibility to furnish medical care regardless of ability to pay, and that patients should discuss their economic as well as their medical problems with their physicians.

8. The California Medical Association and its component county medical societies shall initiate and maintain a continuous program of *professional* education on the following general points:

(*a*) That indemnity-type health insurance is best for both patient and physician, but that it can be made to work only if each physician forego the traditional practice of setting his fee on the basis of ability to pay and, instead, accept the trend toward, and adopt, the principle of a uniform, individual fee list.

(*b*) That the individual fee list will serve its purpose only if both its existence and its level are known to the patient; and that it is the physician's responsibility to inform his patient of these facts.

(*c*) That the fee list will fail to serve its purpose unless it be adhered to irrespective of the possession by the patient of health insurance.

(*d*) That no form of voluntary health insurance can succeed unless the physician cooperate to eliminate abuse and overuse; the physician must forever remember that, whether the check he receives be signed by insurance company or patient, it is the patient's money that is paying the whole bill.

9. County medical societies shall be encouraged to authorize and approve the arrangement of agreements between groups of physicians on one hand and insured groups on the other whereby the cooperating physicians agree to furnish care to members of the insured groups at rates for professional charges fixed by the community fee list. To be eligible for approval by any component county society, such an arrangement must be open to participation by all physicians, and must be under an insurance contract whose provisions meet such standards as the California Medical Association shall from time to time determine.

These, then, are your committee's recommendations for the steps we believe the medical profession must take if sound voluntary health insurance is to be. Their effect should be to create an environment in which voluntary health insurance may grow to a stature which will make unnecessary any form of state-managed, compulsory health insurance.

It should at this point be clear that we regard this problem of health insurance as one whose solution is a task for the medical profession as a whole, and not one which may be handed to California Physicians' Service with the demand that that organization find the answers. As Dichter implies, that kind of past action has made C.P.S. the whipping boy who has had to take the punishment which should instead have been visited on all of us.

We should emphasize, too, that the recommendations so far made do not limit the cooperation of the medical profession to that with any specific insuror. Your committee believes that our profession must take the position that the field of health insurance underwriting is open to any reputable insurance company whose insurance plan and operations meet reasonable standards which are equally applicable to all.

Your committee, however, reaffirms its belief (stated in its interim report) that the organized medical profession must maintain an instrument in the field of health insurance. Our reasons for so deciding we believe remain valid, whatever the type of health insurance is decided to be best for patient and physician. It remains, then, for us to decide what role this, our instrument, should play, and how it should be organized and function best to fulfill its assigned mission.

The primary decision to be made is the answer to the question all of us have so many times asked ourselves: What is the objective of California Physicians' Service? In our interim report, we gave a four-point objective to which, within its limitations, we still subscribe. But those points might better be

considered as purposes rather than an objective. We should now be ready to broaden, and at the same time to condense, that statement of purposes to this single sentence: "The objective of California Physicians' Service shall be to serve as the instrument by which the organized medical profession of California can fulfill its obligation to lead in devising sound ways to apply the insurance method to the costs of private medical care."

There are two big problems of California Physicians' Service which can now be examined in terms of this objective: (1) Better integration of C.P.S. with the California Medical Association and (2) conversion of its insurance program to one which is consistent with the conditions we have described as those which we believe sound health insurance must meet.

A good step toward this integration has already been taken by adding three councilors of the C.M.A. to the Board of Trustees of C.P.S. But, more obviously to indicate that C.P.S. is truly a member of the family of organized medicine and, at the same time, to lessen confusion and streamline operations, your committee recommends that the C.P.S. House of Delegates be abolished, and that all its functions be transferred to the House of Delegates of the California Medical Association. For the same reasons, we further recommend that the Council of the C.M.A. act as a nominating committee for C.P.S. trustees, and that nomination of trustees be made sufficiently far in advance of election to allow time for adequate consideration by the House. We are informed by legal counsel that both these recommendations are possible of accomplishment.

The problem of conversion of the C.P.S. insurance program is more complicated. Anyone who assumes the task of advocating change must remember that California Physicians' Service is a going concern that has done a truly good job in the face of many difficulties. It still remains the largest individual carrier of health insurance in California, with commitments far into the future. And, most importantly, it still is "the doctors' plan."

In the light of these considerations, we recommend that California Physicians' Service organize a subsidiary corporation, qualified under the insurance laws of California to write indemnity type health insurance.

By recommending a separate program operating under a subsidiary corporation, and thus not affecting present C.P.S. operations, we believe that the average-fee plan will have a chance for gradual evolution as its practical problems become demonstrated by experience. If the future substantiates our belief that the average-fee plan will more nearly meet the criteria of good health insurance for both patient and physician, gradual conversion of the C.P.S. program to that plan will be both sound and automatic. At the same time, this method of parallel operation of both indemnity- and service-type plans will avoid the dislocation of a sudden alteration in C.P.S. policy, and, if conversion to the average-fee plan eventually does occur, it will be to a tried and proven insurance program.

These, then, are our major recommendations. May we point out, too, that we are only recommending, and that the full implementation of our recommendations is contingent upon many separate decisions and activities, each of which is a problem by itself. The success of the program we propose will be the sum of the wisdom of these decisions, and the energy with which their objective is pursued.

We of your committee believe strongly that it is neither impractical nor utopian to base the ideal plan of health insurance on the certainty of adherence by the medical profession to the fundamental principle of ethics that the welfare of the patient is the first concern of medicine. We are confident that the result of the application of our conclusions and recommendations will vindicate and confirm that belief.

SPECIFIC RECOMMENDATIONS

(See action on recommendations, page 79)

Your committee recommends:

1. That the House of Delegates of California Physicians' Service be abolished and its functions be transferred to the House of Delegates of the California Medical Association.

2. That the Council of the California Medical Association serve as the nominating committee for California Physicians' Service Trustees.

3. That the Board of Trustees of California Physicians' Service organize and finance a subsidiary non-profit corporation qualified under the insurance laws of California to write indemnity-type health insurance.

4. That each individual physician be urged to accept the principle of individual uniformity of fees, and to formulate an individual fee-list to which, in the absence of agreement with his patient to do otherwise, he will adhere.

5. That each component county medical society of the California Medical Association or its branches be urged to formulate and regularly revise a fee list whose basis shall be the average fee charged the average patient by the average physician in its county.

6. That the California Medical Association formulate a state fee list, which shall be a composite of county lists, and which may be adopted by any county as its list in lieu of a locally determined one. The purpose of county and state fee lists shall be to serve as guides to insurors in formulating realistic indemnity schedules.

7. That the California Medical Association establish machinery on a statewide or regional basis to handle fee-complaints, which machinery shall be available to all patients whether or not they hold health insurance and, if they do, irrespective of the identity of the insuror.

8. That the measure of the legitimacy of a fee-complaint shall be: Whether or not the fee is consistent with the individual fee-list of the physician concerned; and, if the fee charged *is* a departure from the physicians' fee-list, whether or not there had been prior agreement to this departure.

9. That the fee-complaint machinery include a mechanism for enforcement of decisions, which mechanism specifically shall include the provision of expert testimony by the fee-complaint committee in any litigation to force payment of a fee upon whose legitimacy the committee has ruled.

10. That the California Medical Association and its component county medical societies initiate and maintain a continuous program of public education covering the following general points:

(*a*) The fairness of hospital costs and medical fees.

(*b*) The mirage of full-coverage health insurance; why it is that the individual will pay less for care of minor illness if he pays his doctor direct rather than through an insurance company; and why co-insurance is an essential part of good health insurance.

(*c*) The protection against the cost of serious illness which good indemnity-type health insurance can give, and the degree to which this type of health insurance protects normal, two-party relationships between the patient and his doctor.

(*d*) The fact that most physicians have an individual scale of fees upon which their charges for professional services are based. Information about this fee-list is a legitimate query to be put in advance of accepting service.

(*e*) The existence of fee-complaint machinery in California, and the procedure of appeal in cases of fees believed to be unreasonable.

(*f*) That, irrespective of the existence of individual fee-lists, the medical profession adheres to its centuries-old responsibility to furnish medical care regardless of ability to pay, and that patients should discuss their economic as well as their medical problems with their physicians.

11. That the California Medical Association and its component county medical societies initiate and maintain a continuous program of *professional* education on the following general points:

(*a*) That indemnity-type health insurance is best for both patient and physician, but that it can be made to work only if each physician forego the traditional practice of setting his fee on the basis of ability to pay and, instead, accept the trend toward, and adopt, the principle of an individual fee-list.

(*b*) That the individual fee-list will serve its purpose only if both its existence and its level are known to the patient; and that it is the physician's responsibility to inform his patient of these facts.

(*c*) That the fee-list will fail to serve its purpose unless it be adhered to irrespective of the possession by the patient of health insurance.

(*d*) That no form of voluntary health insurance can succeed unless the physician cooperate to eliminate abuse and overuse; the physician must forever remember that, whether the check he receives be signed by insurance company or patient, it is the patient's money that is paying the whole bill.

12. That county medical societies be encouraged to authorize and approve the arrangement of agreements between groups of physicians on one hand and insured groups on the other, whereby the cooperating physicians agree to furnish care to members of the insured groups at rates for professional charges fixed by the community fee list. To be eligible for approval by any component county society, such an arrangement must be open to participation by all physicians, and must be under an insurance contract whose provisions meet such standards as the California Medical Association shall from time to time determine.

13. That the objective of California Physicians' Service shall be to serve as the instrument by which the organized medical profession of California can fulfill its obligation to lead in devising sound ways to apply the insurance method to the costs of medical care.

14. Finally, that in acting on the report of this committee, the House of Delegates by vote express its opinion on each of the above recommendations, and that, for the purpose of consideration of each subject as a whole and avoidance of inconsistent action, the House vote on the various recommendations in the following groupings:

1. Recommendations one and two.
2. Recommendation three.
3. Recommendations four, five, and six.
4. Recommendations seven, eight, and nine.
5. Recommendations ten and eleven.
6. Recommendation twelve.
7. Recommendation thirteen.

That those recommendations voted on favorably by the House and requiring implementation be considered and deemed referred to the Council and to the Board of Trustees of California Physicians' Service for such action by either body as may be proper or for return to the House of Delegates with specific proposals for implementation if it be necessary that the House act thereon.

ACTION BY HOUSE OF DELEGATES

The first three of the specific recommendations were passed by the House of Delegates upon recommendation of Reference Committee No. 1 to which the entire report had been referred for consideration.

As to the specific recommendations Nos. 4 through 13, the report of Reference Committee No. 1, which was adopted by the House of Delegates, was as follows:

"This Committee has reviewed recommendations 4 through 13 of the C.M.A.-C.P.S. Study Committee. This Committee is in agreement with these proposals in general but the Committee feels that these proposals entail some basic changes in the practice of medicine which should be discussed in the component county medical societies. We, therefore, feel that no action should be taken on these matters at the present time. We recommend that each delegate submit these proposals to his county medical society for discussion at the earliest opportunity.

"It is the opinion of this Committee that any local county medical society could institute this program in its own society at any time should it wish to do so. This Committee feels that specific action on these recommendations by the House of Delegates of the California Medical Association at this time would be premature and should be delayed until the next session by which time each component county medical society will have had ample time to study and discuss the proposals and to instruct its delegates in what action it desires to have taken.

"Your Committee recommends to the Council that arrangements be made to provide speakers to local county medical societies on the subject of the C.M.A.-C.P.S. Study Committee Report if any local county medical society requests such additional clarification.

"The Committee invites any comment, discussion, or constructive criticism of the C.M.A.-C.P.S. Study Committee Report between now and the next session of the House of Delegates, at which time this committee will submit its final report."

NOTE: *Please address all communications to the chairman of Reference Committee No. 1—Douglass H. Batten, M.D., 233 A Street, San Diego.*

Diagnosis and Detection

A Statement of Policy by the Cancer Commission of the California Medical Association

Diagnosis is the cornerstone of modern clinical medicine. It requires accurate observation and rational deduction. In its most complete form it is the process of identifying a disease by consideration of the history, symptoms, physical signs, and the results of every other type of examination of the patient. It includes differential diagnosis, and provides a basis for prognosis. Even in the best of circumstances, it may contain an element of uncertainty, so that diagnosis might be defined as "The procedure of reaching the most probable conclusion based on the facts at hand."

Detection is a step toward diagnosis. It is essentially the effort to discover evidence of disease in persons both asymptomatic and symptomatic. Detection requires accurate observation and rational deduction. The clinician detects and evaluates abnormal physical signs; the pathologist detects and evaluates an abnormality in a cell under the microscope; the radiologist detects and evaluates an abnormal shadow in an x-ray film.

Diagnostic and detection procedures may be performed on an individual basis or on a mass basis. They are performed on an individual basis in everyday clinical office and hospital practice. They are performed on a mass basis in military induction stations, large educational and business establishments, and in certain clinics and institutions.

There are now modern techniques at the disposition of the medical profession by which shortcuts may be made in diagnosis. These include certain serological tests for syphilis, cutaneous tests for tuberculosis, x-ray tests for pulmonary disease and cytologic tests for neoplastic disease. All of these tests require the use of various types of laboratory equipment, the cooperation of technicians, and the *interpretation by physicians.* For example, a chest x-ray does not read itself; it requires interpretation by a trained physician; interpretation of a chest film for the purposes of reaching a decision as to whether or not disease appears to be present is a part of diagnosis. That is, a chest x-ray or a vaginal smear for screening or survey purposes *is a diagnostic procedure.*

It is essential for maintenance of quality in medical programs that members of organizations such as the American Cancer Society keep in mind the fact that there is no distinction between diagnosis and detection when the objective of the procedure is the identification of health or disease. Detection procedures are fundamentally medical procedures which should be performed by or under the direction of physicians, and which require supervision and interpretation by physicians. Confusion has been created in the past by referring to detection methods as non-diagnostic or non-professional procedures. Anyone who has seen the distressing results of misinterpretation of chest films and cytologic smears is doubly conscious of the need for emphasizing that detection is a part of diagnosis, and not some mechanical or technical process which can safely be relegated to lay persons.

Council Meeting Minutes

Tentative Draft: Minutes of the 396th Meeting of the Council, San Francisco, November 15-16, 1952.

The meeting was called to order by Chairman Shipman at 9:30 a.m., Saturday, November 15, 1952, in Room 220 of the Hotel St. Francis, San Francisco.

Roll Call:

Present were President Alesen, President-elect Green, Speaker Charnock, Vice-Speaker Bailey, Councilors West, Wheeler, Loos, Sampson, Morrison, Dau, Ray, Montgomery, Bostick, Pollock, Frees, Carey, Shipman, Varden, Heron and Lum, and Secretary Daniels. Councilor Kirchner was absent for cause on November 15 but present November 16.

Absent for cause: Editor Wilbur.

A quorum present and acting.

Present by invitation during all or a part of the meeting were Messrs. Hunton, Thomas, Gillette, Clancy and Pettis of C.M.A. staff, legal counsel Howard Hassard, county society executive secretaries Waterson, Watson, Nute, Thompson; Doctor Wilton L. Halverson, State Director of Public Health; Doctor Dwight H. Murray, legislative chairman; Doctor Francis T. Hodges, secretary of California Physicians' Service; Doctor Leslie B. Magoon of the C.P.S. Study Committee; Ned Burman of public relations counsel; Ben Read of the Public Health League of California; Doctor A. E. Larsen, medical director of C.P.S.; Doctor Frank Wilson, director of the Washington office of the American Medical Association, Doctors H. Gordon MacLean and Berthel Henning; Doctors Earl Longley and Emil Gough of the San Joaquin County Medical Society; Mr. T. D. O'Dea and Mr. Marshall Virello of C.P.S.

1. *Minutes for Approval:*

(a) On motion duly made and seconded, minutes of the 395th Council meeting, held September 6, 1952, were approved.

(b) On motion duly made and seconded, minutes of the 234th meeting of the Executive Committee, held October 19, 1952, were approved, it being noted that the Council gave more than a three-fourths vote of approval to the appropriation of funds for office improvements.

2. *Membership:*

(a) A report of membership as of November 14, 1952, was presented and ordered accepted.

(b) On motion duly made and seconded, 136 delinquent members whose dues had been received were voted reinstatement as active members.

(c) On motion duly made and seconded, in each instance, 11 applicants were granted Associate Membership. These were: Velva V. Brown, Samuel N. Etheredge, Gerald Hirschber, Frank Moore, Jr., and Nadine Foreman, Alameda-Contra Costa; Stephen Cheu, Isle Vivien Collet, Thomas Fuson, and Jerome Radding, Fresno County; Joseph J. A. McMullin, Riverside; Thelma M. Quinn, Santa Clara County.

(d) On motion duly made and seconded in each instance, five applicants were granted Retired Membership. These were: James H. McGranahan, Joseph H. Robinson, and Herbert A. Rosenkranz, Los Angeles; Earl N. Greenwood, San Francisco; Franz Gehrels, San Mateo.

(e) On motion duly made and seconded in each instance, reduction of dues because of illness or postgraduate study was granted seven members.

3. *Veterans' Problems:*

Dr. Berthel Henning, by invitation, discussed some problems confronting the American Legion in looking after the interests of veterans and suggested the Association maintain a committee to discuss such matters with the American Legion. It was agreed such a committee be appointed by the chairman.

4. *C.P.S. Study Committee:*

Dr. Wilbur Bailey, chairman of the C.P.S. Study Committee, reported on considerations recently given several items by the committee. He suggested a basic contract by C.P.S. to eliminate many public and administrative problems now arising from a multiplicity of outstanding contracts. He also suggested that patients be advised on the sums paid to physicians and that a closer liaison be maintained between C.P.S. and the C.M.A.

Dr. Leslie Magoon, a member of the committee, presented the tentative final report of the committee and suggested it be placed before the Interim Session of the House of Delegates, to lie on the table for action at the 1953 Annual Session.

On motion duly made and seconded, it was voted that the Council accept the report presented by Dr. Magoon, authorize the committee to review, condense, modify, if desired, and generally put it into proper form for presentation to the House of Delegates and provide copies for distribution after the report has been delivered.

5. *Medical Services Commission:*

Dr. Leslie Magoon, chairman of the Medical Services Commission, reported the commission is working on several matters concerning the establishment of objectives and machinery for implementing them. Dr. Bailey suggested that the files and other material of the C.P.S. Study Committee be turned over to the Medical Services Commission.

6. *California Physicians' Service:*

Dr. Francis T. Hodges, secretary of California Physicians' Service, reported that C.P.S. was working on uniformity in its contracts, had revoked the physician memberships of five physicians and had approved the payment of a brokerage fee in certain instances. As of September 30, 1952, he reported 672,524 beneficiary and 10,956 physician members.

Mr. Thomas D. O'Dea, at the invitation of Chairman Shipman, discussed the enrollment problems facing California Physicians' Service.

7. *Financial:*

A report on bank balances as of November 14, 1952, was presented and ordered filed.

8. *Disciplinary Proceedings:*

(a) A report from the Los Angeles County Medical Association, relating to the expulsion of a member following a disciplinary hearing, was presented and ordered filed.

(b) Mr. Hassard presented suggested by-law amendments which would create Judicial Councils in the larger county societies for the sole purpose of handling all disciplinary proceedings. On motion duly made and seconded, it was voted to place these amendments before the Interim Session of the House of Delegates.

9. *C.P.S. Fee Schedule Committee:*

After discussion, it was agreed that the work of the C.P.S. Fee Schedule Committee should be integrated with the Medical Services Commission and that a vacancy on the committee remain unfilled at this time.

10. *Committee on Public Health and Public Agencies:*

Dr. Wilton L. Halverson, State Director of Public Health, reported on a meeting held by representatives of his department with Drs. West, Loos and Carey, members of the Committee on Public Health and Public Agencies, on November 13. Dr. West then presented the subjects under discussion.

(a) On motion duly made and seconded, it was voted to refer to the Committee on Public Policy and Legislation and to the public relations department proposed legislation to promote better control of rabies through dog licensing, safeguards within dog pounds, tagging of rabies-inoculated dogs and other measures.

(b) Discussion was held on proposed amendments to the Agriculture Code to prohibit the sale of raw milk except where cows' milk is certified or goats' milk guaranteed. On motion duly made and seconded, it was voted to approve such amendments in principle, subject to their being submitted to the legislative and public relations committees.

(c) It was agreed to ask the Committee on Rural Health to make plans for meeting with boards of supervisors and other officials in order to effectuate better public health measures in some rural "playground areas" where full-time public health departments are not maintained and where seasonal visitors create sanitation and other public health problems.

(d) Discussion was held on the Crippled Children's Program, especially with a view toward Dr. Halverson's expressed wish for a complete decentralization and county administration of the plan. Mention was made of interim committees in both the State Senate and the Assembly, studying this matter.

(e) Mr. Hassard and Dr. Halverson discussed the present clinic licensing law and suggested amendments to modernize the law and to provide a greater effectiveness of administration in those offices which should be within the scope of this law.

(f) It was agreed to refer to the legislative committee some proposed amendments to the laws governing the use of animals in medical research.

(g) On motion duly made and seconded, it was voted to request the officers of the appropriate scientific sections to cooperate with the Department of Public Health in effecting changes which would permit the use of additional medications in treating the eyes of the newborn.

11. *Legal Department:*

Mr. Hassard reported that briefs are being prepared in the appeal of the San Diego litigation and that oral arguments before the appeals court will probably not be scheduled until next summer. He also reported on a correction in testimony which has been forwarded to the President's Commission on the Health Needs of the Nation. Mr. Hassard also stated that a chiropractic initiative measure is now being circulated and may qualify for the 1954 general election ballot or an earlier special election should such be called.

12. *Public Relations:*

Mr. Clancy urged a closer liaison between the Association and C.P.S., especially in matters of public relations and advertising. On motion duly made and seconded, it was voted to call this to the attention of the Board of Trustees of C.P.S.

13. *Advisory Planning Committee:*

Mr. Hunton reported on the meeting of the Advisory Planning Committee held November 13. A closer liaison with C.P.S. was agreed upon as a necessity at that time. The committee also agreed that the public relations and advertising aids produced by the Association, with the cooperation of the Advisory Planning Committee, should be offered

equally to all county societies but that projects of a local nature should remain the responsibility of the county society itself. Mr. Hunton also discussed a "Health Record" pamphlet which has been devised for offering to parents for the maintenance of a health record on their children. Members of the Advisory Planning Committee are discussing this pamphlet with their respective county societies, with a view toward distribution of the pamphlet when and if it is approved.

14. *Benevolence Committee:*

On motion duly made and seconded, it was voted to approve the proposed policy of the Benevolence Committee which would provide for the contribution of funds on the basis of individual case requirements, with the understanding that state old-age funds would be sought by all those eligible to receive them.

15. *A.M.A. Judicial Council:*

On motion duly made and seconded, it was voted to request the president to confer with the Judicial Council of the American Medical Association on rulings recently handed down by that body on the question of contact with practitioners of other healing arts.

16. *Physician Placements:*

Discussion was held on a proposal of the Santa Clara County Medical Society for the location of physicians in rural areas. On motion duly made and seconded, it was voted to refer this matter to the Committee on Rural Health.

17. *Committee on Industrial Accident Commission:*

Mr. Hassard reported that a new petition has been filed with the Industrial Accident Commission on behalf of the Association, asking for the assumption of authority to make and enforce a medical and surgical fee schedule and offering such a schedule for consideration.

18. *Cancer Commission:*

Report was made on several so-called cancer cures for which the authors make claims not adequately supported by scientific evidence. On motion duly made and seconded, it was voted to request the Cancer Commission to accept jurisdiction in cases of this character, to study the material submitted and to make reports on its findings.

19. *Association Mailing List:*

It was moved, seconded and voted to refer to a special committee of Drs. Arthur Kirchner and L. A. Alesen the question of reviewing an insurance policy whose underwriters seek to use the Association's mailing list in soliciting business.

20. *California Medicine:*

On motion duly made and seconded, it was voted to appoint Dr. James E. Reeves of San Diego and Dr. John G. Walsh of Sacramento as members of the Editorial Board of CALIFORNIA MEDICINE, representing general practice.

21. *Public Policy and Legislation:*

Mr. Ben Read and Dr. Dwight H. Murray reported on the recent state and national elections. It was agreed that Dr. Murray's committee would meet shortly with Dr. Bullock's special Committee on Psychology and it was regularly moved, seconded and voted that Dr. Bullock attend the A.M.A. Interim Session in Denver, to confer with a committee studying the problem of licensing or registering psychologists.

On motion duly made and seconded, it was voted to express to the family of the late Dr. Anthony B. Diepenbrock the extreme appreciation of the Association of the valuable contribution made by him as a member of the Committee on Public Policy and Legislation and in other Association activities.

22. *Doctor Draft Law:*

Dr. West called attention to some of the provisions of the present "Doctor Draft Law" which are discriminatory against certain physicians whose wartime service is not now recognized as credit in determining their position in Selective Service. Mr. Hunton was instructed to take up this matter with the Washington office of the American Medical Association.

23. *General Practitioner of the Year:*

On motion duly made and seconded, it was voted to submit to the American Medical Association the name of Dr. C. C. Violette of Santa Ana as a nominee for selection as the General Practitioner of the Year.

24. *Committee on Problems of the Aging:*

On motion duly made and seconded, it was voted to appoint Dr. Douglas G. Campbell, chairman, and Drs. Elizabeth Mason Hohl and Howard Naffziger members of a special committee on Problems of the Aging.

Adjournment:

There being no further business to come before it, the meeting was adjourned at 5:45 p.m., Sunday, November 16, 1952.

SIDNEY J. SHIPMAN, M.D., *Chairman*
ALBERT C. DANIELS, M.D., *Secretary*

In Memoriam

BLATHERWICK, ALEX A. Died in Los Angeles, November 1, 1952, aged 71, of cerebral thrombosis. Graduate of Rush Medical College, Chicago, Illinois, 1909. Licensed in California in 1911. Doctor Blatherwick was a member of the Los Angeles County Medical Association, the California Medical Association, and the American Medical Association.

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CLEAVE, DAVID C. Died in San Francisco, September 27, 1952, aged 47, of coronary infarction. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1931. Licensed in California in 1931. Doctor Cleave was a member of the Monterey County Medical Society, the California Medical Association, and the American Medical Association.

✤

CONLEY, WILLARD T. Died in Los Angeles, November 15, 1952, aged 67, of terminal pneumonia. Graduate of Northwestern University Medical School, Chicago, 1913. Licensed in California in 1928. Doctor Conley was a member of the Los Angeles County Medical Association, the California Medical Association, and the American Medical Association.

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DELAHOUSSAYE, ALTHEMUS J., JR. Died in Riverside, November 2, 1952, aged 34. Graduate of Howard University College of Medicine, Washington, D. C., 1942. Licensed in California in 1950. Doctor Delahoussaye was a member of the Riverside County Medical Association, the California Medical Association, and the American Medical Association.

✤

EMERSON, MARK L. Died in Oakland, November 11, 1952, aged 80, of thrombosis in the coronary artery. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1899. Licensed in California in 1902. Doctor Emerson was a member of the Alameda-Contra Costa Medical Association, the California Medical Association, and the American Medical Association.

✤

GLENN, ROBERT A. Died in Oakland, November 13, 1952, aged 65, of nephrosis, atherosclerosis and hypertension. Graduate of the University of Pennsylvania, School of Medicine, Philadelphia, 1911. Licensed in California in 1915. Doctor Glenn was a member of the Alameda-Contra Costa Medical Association, the California Medical Association, and the American Medical Association.

✤

HARRIS, FRANKLIN I. Died in Palo Alto, November 13, 1952, aged 57, of coronary thrombosis. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1921. Licensed in California in 1921. Doctor Harris was a member of the San Francisco Medical Society, the California Medical Association, and the American Medical Association.

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HOPKINS, MARK F. Died in San Jose, October 28, 1952, aged 74, of coronary artery disease. Graduate of the College of Physicians and Surgeons, 1903. Licensed in California in 1903. Doctor Hopkins was a retired member of the Santa Clara County Medical Society, the California Medical Association, and an associate member of the American Medical Association.

MCGREER, CHARLES F. Died in Martinez, November 14, 1952, aged 45, of recurrent coronary thrombosis, due to coronary arteriosclerosis. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1942. Licensed in California in 1942. Doctor McGreer was a member of the Alameda-Contra Costa Medical Association, the California Medical Association, and the American Medical Association.

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MELLINGER, HERBERT V. Died October 28, 1952, aged 73. Graduate of Rush Medical College, Chicago, Illinois, 1906. Licensed in California in 1919. Doctor Mellinger was a retired member of the Los Angeles County Medical Association, and the California Medical Association.

✤

MIZE, GUY H. Died October 14, 1952, aged 70. Graduate of Cooper Medical College, San Francisco, 1906. Licensed in California in 1906. Doctor Mize was a retired member of the San Francisco Medical Society, and the California Medical Association.

✤

MOKLER, VICTOR A. Died in Los Angeles, November 2, 1952, aged 60, of coronary occlusion. Graduate of Creighton University School of Medicine, Omaha, Nebraska, 1915. Licensed in California in 1941. Doctor Mokler was a member of the Los Angeles County Medical Association, the California Medical Association, and the American Medical Association.

✤

MURRAY, JOHN J. Died in Glendale, November 2, 1952, aged 54. Graduate of Deutsche Universitat Medizinische Fakultät, Prague, Czechoslovakia, 1923. Licensed in California in 1940. Doctor Murray was a member of the Los Angeles County Medical Association, the California Medical Association, and the American Medical Association.

✤

QUINN, VINCENT J. Died in Los Angeles, November 8, 1952, aged 49, after being shot by a rampaging assailant who did not know him. Graduate of St. Louis University School of Medicine, Missouri, 1927. Licensed in California in 1928. Doctor Quinn was a member of the Los Angeles County Medical Association, the California Medical Association, and the American Medical Association.

✤

SPENCER, ALFRED G. Died October 23, 1952, aged 50. Graduate of the University of Nebraska College of Medicine, Omaha, Nebraska, 1932. Licensed in California in 1932. Doctor Spencer was a member of the San Francisco Medical Society, the California Medical Association, and the American Medical Association.

✤

WALKER, GEORGE W. Died in Pacific Grove, November 1, 1952, aged 76. Graduate of Barnes Medical College, St. Louis, Missouri, 1897. Licensed in California in 1901. Doctor Walker was a retired member of the Fresno County Medical Society, the California Medical Association, and an associate member of the American Medical Association.

NEWS & NOTES

NATIONAL · STATE · COUNTY

ALAMEDA

Dr. John W. Gofman, associate professor of medical physics, University of California, Berkeley, was one of ten recipients of *Modern Medicine* Awards for Distinguished Achievement for 1953. Dr. Gofman was recognized for studies on the part lipoproteins play in the cause of atherosclerosis, said Dr. Walter C. Alvarez, editor-in-chief of *Modern Medicine*, who announced the awards.

FRESNO

Officers of the **Fresno County Medical Society** for 1953 are: President, Dr. William N. Knudsen; president-elect, Dr. Fred E. Cooley; vice-president, Dr. C. H. Covington; secretary-treasurer, Dr. Joseph Logan. Dr. Knudsen succeeded Dr. Kendall B. Holmes as president.

LOS ANGELES

The Fifth Annual Mid-Winter **Radiological Conference** sponsored by the Los Angeles Radiological Society will be held at the Ambassador Hotel, Los Angeles, Saturday and Sunday, February 21 and 22, 1953. Out-of-state speakers will be Dr. Fred J. Hodges, Dr. H. Dabney Kerr and Dr. Ira H. Lockwood.

A banquet preceded by cocktails will be held at the Ambassador Hotel on Saturday evening, February 21. Hotel reservations should be made as soon as possible through the Convention Manager, Ambassador Hotel, Los Angeles.

Conference reservations may be made through Dr. M. M. Haskell, 615 Times Building, Long Beach 2, California. The Conference fee is $20 and dinner will be $6 per plate. Courtesy cards are available to radiological residents and radiologists in military service by pre-registration.

At the November meeting the following **officers of the Los Angeles Radiological Society** for the coming year were elected: president, Dr. John B. Hamilton, Glendale; vice-president, Dr. Walter L. Stilson, Los Angeles; secretary, Dr. Joseph F. Linsman, Beverly Hills; treasurer, Dr. M. M. Haskell, Long Beach. Dr. Harold P. Tompkins, Los Angeles, was elected to the executive committee.

* * *

The Second Annual **Obstetrical Gynecological Forum,** sponsored by the Los Angeles Obstetrical Gynecological Society, will be held at the Elks Club on February 14 and 15. All interested, licensed physicians are welcome. An outstanding program by prominent authorities, including N. S. Assali of Cincinnati, Bayard Carter of Durham, M. Edward Davis of Chicago, Ludwig Emge of San Franciso, and Robert H. Williams of Seattle is planned. Physicians in general practice will receive credit from their Academy for attending this symposium.

Reservations may be made with Dr. John Gaspar, 6253 Hollywood Boulevard, Hollywood.

The Research Study Club of Los Angeles has announced its 22nd annual mid-winter **clinical convention in ophthalmology and otolaryngology** will be held in Los Angeles January 19-30. A special course in surgery of the eye will be given January 23-25. Guest lecturers for the ear-nose-throat section will be Dr. James H. Maxwell, Ann Arbor, Michigan, and Dr. Harry P. Schenck, Philadelphia; and for the eye section, Dr. Ramon Castroviejo of New York City, Dr. Alfred Edward Maumenee, Jr., of San Francisco, and Dr. Meyer Wiener of Coronado. Dr. Wiener will conduct the course on surgery of the eye, which is limited to 24 students.

Further information may be obtained from Dr. Pierre Violé, 1930 Wilshire Boulevard, Los Angeles 5.

* * *

Dr. Paul D. Foster was elected president of the Los Angeles County Medical Association in elections held late last year. Dr. Foster, secretary last year, succeeds Dr. Wilbur Bailey, who was elected trustee of the association. Others elected for 1953 are Dr. Verne C. Crowl, vice-president, and Dr. Ewing L. Turner, secretary-treasurer.

* * *

Dr. Duane W. Bradley of Kelseyville was elected president of the Mendocino-Lake County Medical Society for 1953 at a recent meeting of the organization, and Dr. James B. Massengill of Ukiah, who was president last year, was elected vice-president. Dr. Olga Miller of Talmage was elected secretary-treasurer.

SAN DIEGO

Medical veterans of San Diego County organized themselves into the San Diego County **Medical Veterans Society** on December 11, 1952. Officers pro tem are: President, Dr. Roy S. Averill; vice-president, Dr. Ira H. Wilson, treasurer, Dr. Gordon D. Skeoch; recording secretary, Dr. Wilton M. Lewis; corresponding secretary, Dr. Clifford L. Graves.

Purpose of the organization is to have a voice in the drafting of the new law that will take the place of Public Law 779 on July 1, 1953. Other activities will depend on developments.

The organizational meeting was addressed by A.M.A. Delegate Sam J. McClendon, Procurement and Assignment Committee Chairman Chester O. Tanner, and A.M.A. Alternate Delegate John B. Price of Santa Ana.

SAN FRANCISCO

Dr. Edmund J. Morrissey, president-elect of the San Francisco Medical Society in 1952, has been installed as president for 1953. Dr. Samuel R. Sherman was elected president-elect, Dr. Helen Starbuck vice-president, Dr. Herbert C. Moffitt, Jr., secretary-treasurer and Dr. Robert C. Combs assistant secretary-treasurer.

* * *

The Bay Area **Society of Physical Medicine and Rehabilitation** held its initial meeting on November 20, 1952, at Letterman Army Hospital. At present the membership is restricted to physicians specializing in this field. Future meetings will be held the third Thursday evening of each month.

* * *

The annual dinner meeting of the San Francisco Chapter of the **Pan American Medical Association,** honoring the San Francisco Consular Corps and visiting Latin Amer-

ican physicians and students, was held at the Bohemian Club, December 6, 1952. Dr. Charles Pierre Mathé, trustee of the medical organization, presented the society's words of greeting and the Hon. Sr. Carlos H. Palmieri, Consul General of Guatemala, responded. Dr. Robert T. Legge, Professor Emeritus of Hygiene, University of California, spoke on "Occupational Diseases."

The outgoing president of the San Francisco Chapter is Dr. Suren H. Babington. The **newly elected officers** are as follows: President, Dr. J. C. Geiger; first vice-president, Dr. Marius A. Francoz; second vice-president, Dr. Berthel H. Henning; secretary, Dr. Ralph A. Reynolds; treasurer, Dr. Luis A. Chaparro.

* * *

Dr. William Barry Wood, Jr., Busch Professor of Medicine at Washington University School of Medicine, St. Louis, presented the thirteenth course of **Herzstein Medical Lectures** under the direction of Stanford University School of Medicine and the University of California School of Medicine, on December 8, 10 and 12 in Lane Hall. Dr. Wood's subject, "The Cellular Immunology of Acute Bacterial Infections," included lectures on "The Pathogenesis of Bacterial Pneumonia," "Surface Phagocytosis," and "The Cytodynamics of Bacteremia."

SAN MATEO

Officers of the **San Mateo County Medical Society** for 1953 are: President, Alf. T. Haerem of Redwood City; president-elect, Bradley C. Brownson of San Mateo; secretary-treasurer, Jackson T. Flanders of Redwood City. Dr. Haerem, president-elect in 1952, succeeds Dr. Dan W. Boudett as president, and Dr. Flanders fills the position occupied last year by Dr. Brownson.

SANTA CRUZ

Dr. Phillip E. Karleen of Soquel was elected president of the Santa Cruz County Medical Society at a recent meeting. He succeeds Dr. Jerome A. Ludden, Jr., of Watsonville. Dr. Samuel B. Randall was reelected secretary-treasurer.

GENERAL

Voicing concern over the "rapidly expanding and uncontrolled" use in California of electrical **vaporizers for dispensing lindane insecticide** in food establishments for control of flies and other insects, the State Board of Public Health recently went on record opposing the use of such devices. The Board urgently recommended that "electrical vaporizers dispensing lindane or other chlorinated hydrocarbons not be used in closed spaces where people sleep, work or where unpackaged food is exposed, and that extreme caution be exercised in the indoor dispersion of such chemicals by any means."

Dr. Wilton L. Halverson, State Director of Public Health, said the matter of lindane dispensers had confronted the Board for some time and that a study of the problem led to the conclusion that lindane dispensers should be used only under carefully controlled conditions or not at all. The California Conference of Local Health Officers has urged that steps be taken to curtail the present uncontrolled use of such devices. A great variety of lindane dispensers, many of inferior construction, are now in use, Dr. Halverson said.

POSTGRADUATE EDUCATION NOTICES

UNIVERSITY OF CALIFORNIA AT LOS ANGELES SCHOOL OF MEDICINE

UNIVERSITY OF SOUTHERN CALIFORNIA SCHOOL OF MEDICINE

COLLEGE OF MEDICAL EVANGELISTS

Fourth Annual Chest Disease Symposium

Dates: January 22 and 23, 1953, 9:00 a.m.-5:00 p.m.

Fee: $25.00 (includes reception and dinner).

This course is open only to graduates of medical schools approved by the Council on Medical Education and Hospitals of the American Medical Association. The fee for the course is $25.00, payable at the time of enrollment, either by check or money order made payable to the Regents of the University of California. (The Fourth Annual Chest Disease Symposium is presented through the cooperation of the Los Angeles County Tuberculosis and Health Association, the Los Angeles, California and American Trudeau Societies, and the American College of Chest Physicians and sponsored by the University of California at Los Angeles School of Medicine, University of Southern California School of Medicine and College of Medical Evangelists.)

Contact: Applications or requests for information concerning this course should be made to: Thomas H. Sternberg, M.D., Head of Postgraduate Instruction, Medical Extension, University of California, Los Angeles 24, California. Telephone: ARizona 7-4201 or BRadshaw 2-6192.

MEDICAL EXTENSION UNIVERSITY OF CALIFORNIA

Postgraduate Courses for 1953

Cardiovascular Diseases, February 2, 3, 4, 5, mornings. Fee $25.00. Medical Center.

Electrocardiography, February 2, 3, 4, 5, afternoons. Fee $25.00. Medical Center.

Pulmonary Function, February 6, 7, 8, all day. Fee $50.00. Medical Center.

Course for General Practitioners, March 2 through 6, Mount Zion Hospital, San Francisco. Fee to be announced.

Symposia on Psychosomatic Medicine, Wednesday afternoons and evenings, March 11, 18, 25. Fee to be announced. Langley Porter Clinic, San Francisco.

Diagnostic Radiology, April 6, 7, 8, at Franklin Hospital, San Francisco. Fee to be announced.

Pediatric Conference, June 22 through 26. Fee to be announced. Medical Center.

Conference on General Surgery, June 15 through 19. Fee $75.00. Medical Center.

Obstetrical and Gynecological Conference, September 2, 3, 4. Place and fee to be announced.

Ophthalmology (for specialists), September 14 through 19. Fee $75.00. Medical Center.

Medicine for General Practitioners, September through November. East Oakland Hospital. Fee $50.00.

Evening Lectures in Medicine, September through November. Fee $50.00. Mills Memorial Hospital, San Mateo (probably).

Contact: All inquiries to be addressed to Stacy R. Mettier, M.D., Professor of Medicine, Head of Postgraduate Instruction, Medical Extension, University of California Medical Center, San Francisco 22.

STANFORD UNIVERSITY SCHOOL OF MEDICINE

The Stanford University School of Medicine will offer the annual postgraduate conference in Clinical Ophthalmology from March 23 through 27, 1953. The program this year will be devoted to Ophthalmic Surgery.

Registration will be open to physicians who limit their practice to the treatment of diseases of the eye or eye, ear, nose and throat. In order to allow free discussion by members of the conference, registration will be limited to thirty physicians.

Instructors will be Dr. A. Edward Maumenee, Dr. Dohrmann K. Pischel, Dr. Jerome W. Bettman, Dr. Max Fine, Dr. Earle H. McBain, and Dr. Arthur J. Jampolsky.

Programs and further information may be obtained from the Office of the Dean, Stanford University School of Medicine, 2398 Sacramento Street, San Francisco 15, California.

UNIVERSITY OF SOUTHERN CALIFORNIA SCHOOL OF MEDICINE

Division of Medical Extension Education

No. 882—Essential Physics in Radiology

Dates: March 9, 1953, through April 10, 1953—Los Angeles County Hospital April 13, 1953 through May 25, 1953—Cedars of Lebanon Hospital.

Tuition: $55.00.

Speakers: Robert E. Pugh, Jr., F.A.C.R. (Assoc.), Henry L. Jaffe, M.D.

Contact: Dr. Gordon E. Goodhart, Director, Medical Extension Education, 1200 North State Street, Los Angeles 33, Calif., CApital 4195.

THIRD ANNUAL POSTGRADUATE MEDICAL AND SURGICAL CONVENTION

Pioneer Memorial Hospital, Brawley

FRIDAY, FEBRUARY 27, 1953

MORNING—ENDOCRINE DISEASES

1. Gynecological Endocrinology—Dr. Charles E. McLennan, Professor of Obstetrics and Gynecology.
2. Management of Diabetic Patients—Dr. John A. Luetscher, Associate Professor of Medicine. Dr. George Bernard Robson, Associate Clinical Professor of Medicine.
3. Medical Problems of the Thyroid and Adrenal—Dr. John A. Luetscher, Dr. George Bernard Robson.

12 noon—Luncheon

AFTERNOON

1. Surgery of the Endocrine System—Dr. Victor Richards, Assistant Professor of Surgery.
2. Roundtable—Problems in Endocrinology—Dr. John A. Luetscher, Dr. Charles E. McLennan, Dr. Victor Richards, Dr. George Bernard Robson.

EVENING

Banquet—Address: Supervoltage Radiation in the Treatment of Cancer—Dr. Henry S. Kaplan, Professor of Radiology.

SATURDAY, FEBRUARY 28, 1953

MORNING

1. Surgery of the Esophagus and Stomach—Dr. Gunther W. Nagel, Clinical Professor of Surgery.
2. Diagnosis and Treatment of Lesions of the Colon—Dr. Russell R. Klein, Assistant Clinical Professor of Surgery.
3. X-ray Diagnosis of Gastrointestinal Diseases — Dr. Henry S. Kaplan.

12 noon—Luncheon

AFTERNOON

1. Surgery of the Biliary Tract and Pancreas—Dr. Victor Richards.
2. Roundtable—Gastrointestinal Hemorrhage—Dr. Russell R. Klein, Dr. John A. Luetscher, Dr. Henry W. Nagel, Dr. Victor Richards, Dr. George Bernard Robson.

UNIVERSITY OF CALIFORNIA AT LOS ANGELES SCHOOL OF MEDICINE, Medical Extension

Postgraduate Course in Basic Neurology

Date: February 16 to June 8, 1953.

Fee: $75.00.

Instructional Staff: Chairman, R. B. Livingston, M.D., Associate Professor of Anatomy and Physiology, University of California School of Medicine, Los Angeles; Horace W. Magoun, Ph.D., Professor of Anatomy and Chairman of the Department, University of California Medical School, Los Angeles; J. D. French, M.D., Associate Clinical Professor of Surgery, University of California Medical School, Los Angeles; Chief Neurosurgeon, Veterans Administration Hospital, Long Beach.

Contact: Thomas H. Sternberg, M.D., Head of Postgraduate Instruction, Medical Extension, University of California, Los Angeles 24, Calif.

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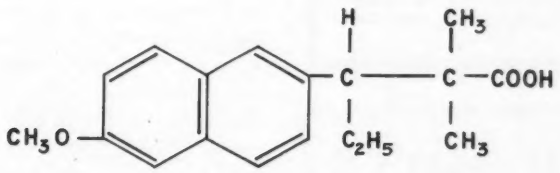

as an effective estrogenic substance with a *strikingly low incidence* of these undesirable side effects.

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SEARLE RESEARCH IN THE SERVICE OF MEDICINE

Say 70 Per Cent of Breast Cancer Cases Can Be Cured

Breast cancer in its early stages detected as a result of the presence of certain conditions and treated by the removal of the entire breast can be expected to yield a cure rate in excess of 70 per cent. This is the opinion of Drs. Calvin T. Klopp, John D. Hoyle and Brian B. Blades, associated with the department of surgery and the cancer clinic of the George Washington University Medical School, Washington.

There are no symptoms of early breast cancer, the doctors wrote in a recent issue of the *Journal of the American Medical Association*. All positive findings are objective signs that can be either seen or felt.

Women and physicians can and should detect cancer of the breast in its early stages by being on the lookout for such conditions which may indicate its presence. These include: (1) persistent scaling of the nipple of the breast; (2) slight ulceration of the nipple; (3) a discharge from the nipple; (4) slight thickening of the breast; (5) a tiny lump in the breast; (6) slight thickening of the nipple, or (7) a nontender lump in the armpit.

"Breast cancer is often described as beginning as a lump, creating the impression that the cancer has been present for a short time prior to the appearance of the lump," the doctors stated. "In certain rapidly growing tumors this may be the case, but it is probably safe to estimate that the breast cancer has been present for several months or possibly for several years before the appearance of the tumor.

"Education of lay persons has sharpened public awareness to minimal, asymptomatic physical changes. Women are being made more aware of and have become conscious of minimal changes in the consistency and appearance of their breasts. Currently, a woman who finds a minute change in a breast will usually present herself for examination without delay, eliminating that prolonged interval so common during the past decade between the appearance of the abnormality of her breast and the consultation with a physician.

"The signs and symptoms of late breast cancer should be as seldom seen as those of leprosy in a general hospital."

Another article in the same issue of the *Journal* discussed various means which physicians may employ for early detection of breast cancer. This article was written by Dr. Otto Saphir, Chicago, associated with the department of pathology, Michael Reese Hospital.

Both articles stated that the most reliable means of diagnosing any lesion of the breast is by biopsy. Surgical biopsy can be easily done, and the correct-

(Continued on Page 50)

Say 70 Per Cent of Breast Cancer Cases Can Be Cured

(Continued from Page 44)

ness of the diagnosis in routine cases is almost 100 per cent, according to Dr. Saphir.

Microscopic examination of secretion from the nipple may lead to early diagnosis of certain types of breast cancer, Dr. Saphir pointed out. Microscopic examination of secretions has proved very successful in the early diagnosis of vaginal and cervical cancers, and such studies should be included as a routine procedure during every complete breast examination, he added.

These two articles are the fourth and fifth in a series of six such reports on cancer which will appear in the *Journal*. Written by cancer specialists, the series is sponsored by the office of the A.M.A.'s Committee on Research of the Council on Pharmacy and Chemistry. Previous articles discussed present-day methods for the earliest possible diagnosis of cancer of the cervix, stomach and lung, and the final one will discuss the care of the hopelessly ill cancer patient.

Read CALIFORNIA MEDICINE'S *Classified Advertising Section for Locations*

Periodic Physical Examination Helps Keep Individual Healthy

An ounce of prevention through a periodic physical check-up is better than a pound of cure, and is the best way to sound health and peace of mind.

Preventive medicine offers the best means of adding years to life and life to years, Dr. Lewis J. Burch, of Mt. Pleasant, Mich., wrote in a recent issue of *Today's Health*, published by the American Medical Association.

Immunization is accepted almost universally and has proved successful as preventive medicine; the periodic health examination is another such effective weapon for safeguarding health, he stated, adding:

"Most of us get used to feeling the way we feel each day. We carelessly disregard those little danger signals that warn of impending trouble. Or we dose ourselves with all kinds of nostrums in an effort to cure or mask the symptoms that annoy us. Sometimes, too late, we find that the little danger has become a big danger."

Physical check-ups, according to Dr. Burch, should be obtained by those between the ages of 15

(Continued on Page 59)

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Periodic Physical Examination Helps Keep Individual Healthy

(Continued from Page 51)

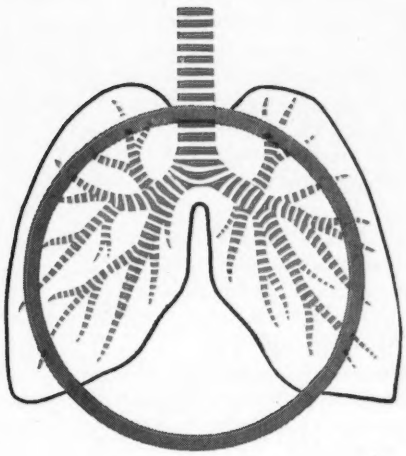
and 35 years every two years, by those 35 to 60 annually, and by those over 60 every six months. However, some individuals may require more frequent examinations, which can be determined by a physician.

Many diseases, such as cancer, tuberculosis and those of the heart, blood vessels and kidneys, would not cause so many deaths in early life if they were diagnosed and treated in the initial stages, Dr. Burch pointed out. One doctor has estimated that each year thousands of Americans would have lived longer if they had known they needed help, or had sought it in time, he added.

The basic physical examination, Dr. Burch stated, should include the entire body: all body openings, the pelvic region, abdomen, breasts, chest, heart, skin, joints, muscles, nerve reactions and blood pressure. Basic laboratory tests that should be made include a urinalysis, blood count, stained smears, and serologic tests for syphilis.

In Bronchial Asthma

—*an Effective Treatment*



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Recent significant reduction in price, and reduced frequency of injections, have increased the economy of ACTH treatment.

ACTH continues to be foremost in the treatment and management of intractable bronchial asthma. ACTH has been dramatic in relieving acute paroxysms of bronchial asthma; periods of complete freedom lasting for several weeks or months have been induced by a single course of ACTH therapy.[1-5]

In 5 patients with chronic intractable asthma treated with ACTH or cortisone, incapacitating attacks were avoided and an asymptomatic state was restored. ACTH seemed to bring about more uniform results than cortisone.[6] "A long-acting preparation of ACTH in gelatin gave the best results and required the smallest dosage."[6]

HP*ACTHAR *Gel*, the new repository ACTH, provides complete convenience and ease of administration in short-term treatment of bronchial asthma.

(1) Bordley, J. E., et al.: Bull. Johns Hopkins Hosp. 85: 396, 1949; (2) Rose, B., et al.: Canad. M. A. J. 62: 6, 1950; (3) Randolph, T. G., and Rollins, J. P.: In Proceedings of First Clinical ACTH Conference, edited by J. R. Mote. Philadelphia, The Blakiston Co., 1950, p. 479; (4) McCombs, R. P., et al.: Bull. New England M. Center 12: 187, 1950; (5) Baldwin, H. S., and DeGara, P. F.: J. Allergy 23: 15, 1952; (6) McCombs, R. P.: New England J. Med. 247: 1, 1952.

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PHYSIOLOGIC THERAPEUTICS THROUGH BIORESEARCH

Says Preventive Medicine Should Encompass Chronic Chest Disease

An important aspect of preventive medicine should be the control of chronic bronchopulmonary disease. It is common, communicable, preventable, and causes enormous economic losses, in the opinion of Dr. Walter Finke, Rochester, N. Y., associated with the chest clinic, Genesee Hospital.

In the United States, at least two to three million persons suffer from chronic bronchopulmonary disease, he wrote in a recent issue of the *Journal of the American Medical Association*. Such afflictions are chronic diseases of the lungs and windpipe, such as bronchitis, asthma and persistent forms of pneumonia.

"Since chronic bronchopulmonary disease often leads to serious complications, such as bronchiectasis, and accounts for enormous economic losses, it should be an important object of preventive medicine," Dr. Finke added.

"A dynamic, prophylactic approach should utilize present knowledge that the disease most frequently originates from inconspicuous respiratory ailments during childhood."

Dr. Finke pointed out that chronic bronchopulmonary disease rivals tuberculosis as a cause for lost manpower, and in terms of production time lost, it exceeds the common cold in importance.

Respiratory infection of recurrent character becomes evident in childhood, he stated, and many sickly children do not outgrow their susceptibility to these sicknesses. It is generally believed, he added, that children acquire most of their respiratory ailments from extrafamilial sources, especially in school.

According to Dr. Finke, children also get such diseases from intimate household contacts, the pattern presenting itself in preschool periods.

"At present, respiratory illnesses are considered by many to be a minor problem," he said. "Surely, thousands of children who a decade ago would have succumbed to pneumonia now survive and apparently are cured after a few days of antibiotic treatment; however, chronic disease often develops following inadequate treatment.

"Although over-all figures on mortality and duration of respiratory sickness may continue to decrease, recent surveys indicate an increase in the incidence of bronchopneumonia and other respiratory illnesses among children. Thus, respiratory infections still present major problems.

"We now have therapeutic agents that, if wisely used, can eradicate most of these childhood respiratory illnesses."

Although continuous administration of penicillin as a prophylaxis is still a controversial issue, Dr. Finke pointed to a study of 100 young children so

(Continued on Page 16)

He's heard the call for VI-DAYLIN®

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Vitamin A	3000 U.S.P. units
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Thiamine Hydrochloride	1.5 mg.
Riboflavin	1.2 mg.
Ascorbic Acid	40 mg.
Vitamin B_{12} Activity (by microbiological assay)	3 mcg.
Nicotinamide	10 mg.

POUR out a shimmering spoonful of VI-DAYLIN . . . notice its unclouded yellow-honey appearance . . . sniff its pleasant, citrus-like odor . . . then *taste* it! That delicious lemon-candy flavor explains why children accept VI-DAYLIN eagerly right from the spoon—and willingly come back for more.

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But take a look at VI-DAYLIN's improved formula. Here, truly, is effective multivitamin therapy. Seven important vitamins in every spoonful—and now three times as much vitamin B_{12}. One 5-cc. teaspoonful daily is the average dose for children up to the age of 12. Mixes with milk, juices and soft foods for infants. Stable without refrigeration. VI-DAYLIN is available at all pharmacies in 90-cc., 8-fluidounce and 1-pint bottles.

Abbott

Says Preventive Medicine Should Encompass Chronic Chest Disease

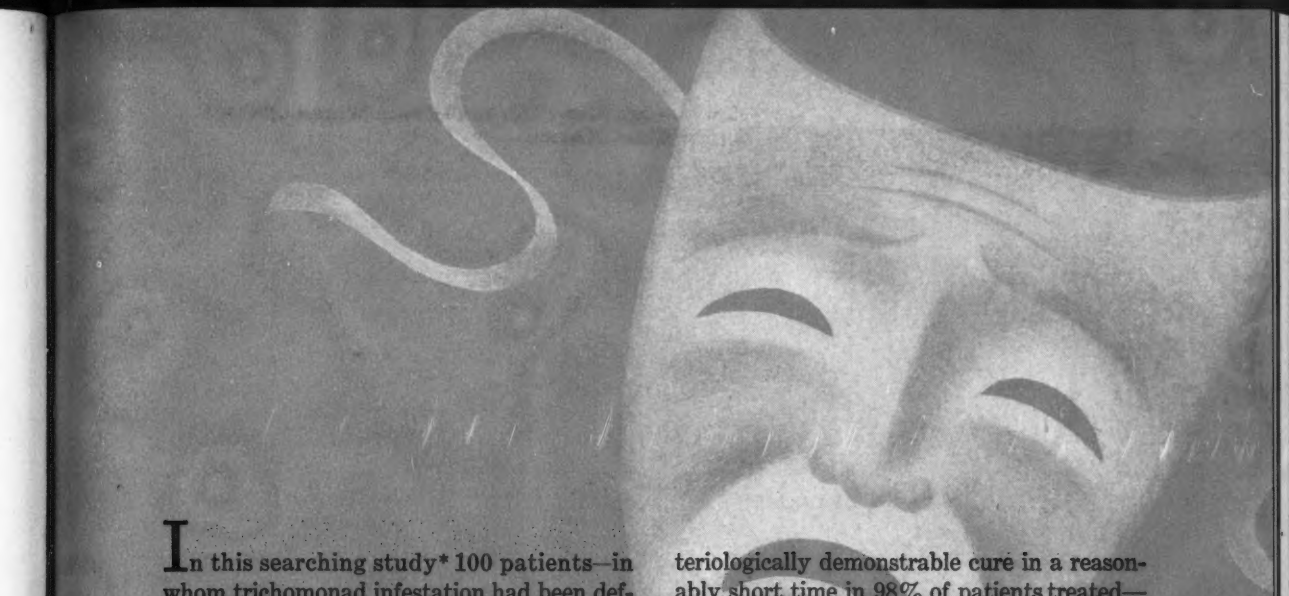
(Continued from Page 10)

treated. It showed that the incidence of disabling and non-disabling respiratory illnesses was 2.5 per child in the 41 treated children, compared with 4.3 in 35 children who were not treated with penicillin and acted as controls. The number of days of respiratory illnesses was 9.3 per child in the treated group, as against 23.8 in the control group.

In a group of older children studied, Dr. Finke reported absenteeism from school averaged 25 days per 1,000 pupil days. In addition to this over-all average, a treated group of children lost only 20 additional days, against 63 days lost by a control group. Only 30 per cent of the 62 children continuously treated with penicillin were absent from school more than three times, compared to 76 per cent of the controls.

"It appears that with the cooperation of the private physician, preschool and school health programs could greatly contribute to the prevention of bronchopulmonary disease," Dr. Finke wrote.

This can be accomplished, he added, by observation of infants born into families in which chronic respiratory disease exists, prompt elimination of significant respiratory infections, and the discovery of chronic cases by the family physician or by routine chest x-rays.



In this searching study* 100 patients—in whom trichomonad infestation had been definitely established—were treated solely with Vagisol Suppositabs (tablet-shaped vaginal suppositories), one suppositab to be inserted high into the vaginal vault twice daily.

72 of these 100 patients were cured in 18 days; 22 in 36 days, 4 in 54 days. Final pronouncement of cure was based on repeated negative cultures.

All of the 98 patients were symptom-free after 2.15 mean patient days on Vagisol, but treatment was continued until cultures were repeatedly negative.

Negative wet smears were not accepted as proofs of cure, since culture frequently proved positive when the wet mount had appeared negative. Thus the hazard of mistaking a temporary remission for a real cure was definitely prevented.

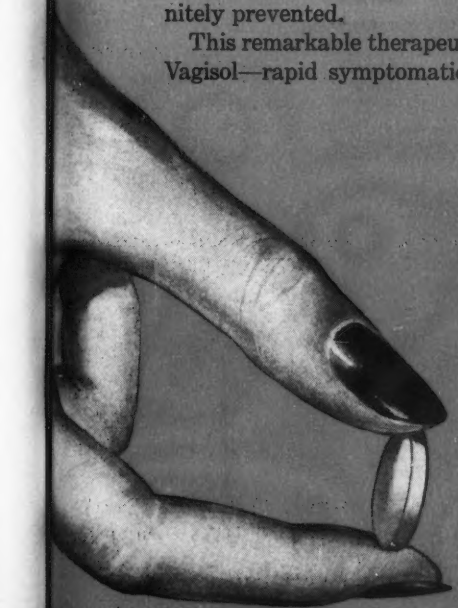
This remarkable therapeutic superiority of Vagisol—rapid symptomatic relief and bacteriologically demonstrable cure in a reasonably short time in 98% of patients treated—is due to the powerful antibacterial and antiparasitic actions of phenylmercuric acetate and tyrothricin, the digestive action of papain, the surface activity of sodium lauryl sulfate, and lactose and succinic acid-induced lowering of the vaginal pH with resultant regrowth of the Doederlein bacillus.

Each Vagisol Suppositab, odorless, nonstaining, and nonirritating, contains:

Phenylmercuric Acetate	3.0 mg.
Tyrothricin	0.5 mg.
Succinic Acid	12.5 mg.
Sodium Lauryl Sulfate	3.0 mg.
Papain	25.0 mg.
Lactose	0.75 Gm.

Supplied in bottles of 36.

For optimal results it is suggested that Vagisol therapy be prescribed for 36 days, with weekly or biweekly check-ups.



Vagisol Suppositabs are available through all pharmacies. Physicians are invited to write for literature and clinical test samples; please address Smith-Dorsey, Lincoln, Nebraska, a Division of The Wander Company.

VAGISOL

SUPPOSITABS

A DORSEY PREPARATION

New Drug May Aid Arthritic; Warn of Toxic Side-Effects

Phenylbutazone (Butazolidin®), a new drug, offers promise in the treatment of rheumatoid arthritis and other similar musculoskeletal disorders, two articles in a recent issue of the *Journal of the American Medical Association* stated.

However, both stressed the fact that the drug can cause serious side-effects, and its use should be limited until further studies of its effects and toxicity have been made. They also stated that it has not been determined as yet whether the drug is truly antirheumatic or only analgesic in its action.

One article, prepared by five Tucson, Ariz., physicians, reported on the results of treating 147 persons suffering from rheumatoid arthritis and rheumatoid spondylitis.

"Phenylbutazone appears to produce striking subjective improvement in a high percentage of rheumatoid spondylitis, and is less effective in peripheral rheumatoid arthritis," they stated. "Objective improvement is less dramatic, but is definite in a small percentage of cases."

Subjective improvement included a marked decrease in pain and stiffness, and an increase in a sense of well-being. Objective improvement included a marked decrease in swelling, an increase in range of motion, and an increase in strength.

Forty-four per cent of the patients suffered toxic side-effects from the drug, some of a rather serious nature, the doctors reported. Because of toxic reactions, it was necessary to discontinue treatment in 11 patients. The untoward effects included blood disorders, salt and water retention precipitating heart failure, the development of ulcer symptoms, rash, swelling, weight gain, nausea and vomiting. Most of the toxic effects subsided upon cessation of use of the drug.

The second article, prepared by five New York physicians, described a study of 200 trials of phenylbutazone and of a combination of phenylbutazone and aminopyrine. The doctors expressed a preference for phenylbutazone alone, as the possible pharmacological hazard of aminopyrine is eliminated.

"Our preliminary observations indicate that these drugs are superior analgesics in the painful, chronic musculoskeletal conditions studied," they pointed out. "So far, our results show that they appreciably surpass the suppression of symptoms provided by salicylates, gentisate and aminopyrine."

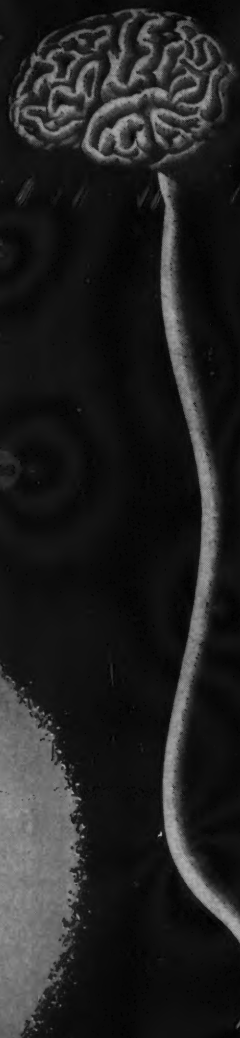
Fifty-one toxic reactions were seen by the New York doctors, who stated that, although none were serious, it became necessary or was deemed advisable to interrupt therapy in 22 of the patients. Most reactions subsided when use of the drug was discontinued.

Both articles reported that the effectiveness of the drug became apparent within a few days. When ap-

(Continued on Page 26)

central nervous "pacifier"...

Mephate



In Mephate 'Robins', the clinical usefulness of mephenesin per os has been significantly heightened by the inclusion of glutamic acid hydrochloride, which improves absorption and enhances effectiveness for many patients otherwise unresponsive.* Provides a relaxant effect on skeletal muscle spasm; an ameliorating effect on tremor; and a relief of anxiety without dimming consciousness. Particularly helpful in abnormal neuro-muscular conditions such as rheumatic disorders, disc syndromes and cerebral palsy; alcoholism, anxiety tension states and psychiatric states.

In each Mephate Capsule, 0.25 Gm. mephenesin — with 0.30 Gm. glutamic acid hydrochloride. Adult dosage starts at 2 capsules 3 or 4 times a day, preferably with food or liquids.

*Hermann, I. F., and Smith, R. T.: JL. Lancet 71:271 (July), 1951.

A. H. ROBINS CO., INC. · RICHMOND 20, VA.

Ethical Pharmaceuticals of Merit since 1878

New Drug May Aid Arthritic; Warn of Toxic Side-Effects

(Continued from Page 22)

preciable benefits were obtained, they rapidly reached a maximum, and improvement remained level throughout the period of treatment. Most patients, it was added, noted a return of symptoms within three days after cessation of therapy.

The Tucson physicians who made one report are Drs. Charles A. L. Stephens, Jr., Elmer E. Yeoman, Paul Holbrook, Donald F. Hill, and William L. Goodin. The New York doctors are Drs. Otto Steinbrocker, Sidney Berkowitz, Mortimer Ehrlich, Mortimer Elkind and Solomon Carp.

First Injunction Under Durham-Humphrey Drug Law. Food and Drug Administration reports the first injunction obtained under the Durham-Humphrey drug law which went into effect last spring. Defendant was the Renesol Corp., of Jersey City, a mail-order drug house, which was permanently enjoined from mailing a phenobarbital, Renesol, without a prescription. The company also will be required to give adequate directions for use. Renesol was promoted for treatment of epilepsy. FDA said its inspectors, who placed orders without mentioning intended use, were supplied with whatever quantity they requested. Directions were said to contain neither recommended dosage nor warning that the drug was habit-forming.

Pentagon Conference Starts Discussions on Doctor Draft Law Extension

(Continued from Page 32)

meet military requirements for long; unless the younger men in Priority IV are made available by a change in the law, the services will be offered too many of the colonel and major age and experience, not enough for the captain and lieutenant commissions. Dislocating physicians of 15 to 20 years' experience from their civilian practice will create additional problems.

3. The age and experience level of Priority IV men make many of them more acceptable, but it is possible that a high percentage already have had two or more years of active military duty; besides, these men can't be called until Priority II has been used up.

4. The professional manpower shortage will continue until 1958, when enough non-veterans, currently deferred from the regular draft to complete their medical training, will be available to meet most military requirements.

No conclusions were reached at the first meeting, and association representatives were not asked to pledge support for an extension of PL 779 at this time.

PREMENSTRUAL TENSION AND DYSMENORRHEA

- headache... backache... malaise
- nervousness... irritability
- abdominal distention
- breast tenderness

A combination of clinically sound anti-edema and analgesia agents, M-Minus 4—

relieves abdomino-pelvic swelling and headache by releasing excess tissue fluids

provides analgesia for the cramps and psychic disturbances often accompanying menstruation

M-Minus 4 contains:
N, N-Dimethyl-N'-(2-pyridyl)-N'-(p-methoxybenzyl) ethylenediamine 8-bromotheophyllinate [Pyrabrom].....50 mg.
Acetophenetidin.....100 mg.
—Bottles of 24 and 100 tablets.

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Arthralgen®

arthralgesic unguent—relieves joint and muscle pain, increases blood flow in rheumatic and muscular disorders, aids in the local treatment of arthritis.

Combines the 3-way synergistic action of (1) Vasodilation (Methacholine chloride 0.25%) (2) Rubefaction (Thymol 1%) and (3) Analgesia (Menthol 10% and Methyl Salicylate 15%) in a highly absorbable ointment base.

Look Into That Persistent Mouth Sore—It May Be Cancer

If you have a sore in your mouth that has persisted for three or four weeks, see your physician. It may be cancer.

Cancer within the mouth accounts for approximately eight per cent of all human malignant diseases, according to Dr. James W. Hendrick, San Antonio, and Dr. Grant E. Ward, Baltimore. The greatest incidence of such cancers is between the ages of 50 and 60 years, with men being affected five times as often as women.

Because of thei raccessibility, such cancers should be diagnosed early and adequate treatment instituted, the doctors wrote in a recent issue of the *Journal of the American Medical Association.* However, the larger percentage, when seen by the tumor specialist, are advanced cases.

Because cancers within the mouth frequently spread to other parts of the body, it is essential not only to eradicate the primary lesion but also to eradicate the involved lymph nodes, which transmit the cancer to other parts of the body, the doctors pointed out.

Microscopic examination of a specimen of the intraoral lesion should be made when persistent sores prevail, they stated. The choice of treatment depends upon the location of the tumor, its size, its extent, the type, the age and general physical condition of the patient, and the lymph node involvement.

These cancers may be treated with irradiation, electrosurgery, surgery, or a combination of these methods, in the opinion of the doctors, who added:

"Recent advances in anesthesia, operative technique, the free use of antibiotics, intranasal feeding during intensive preoperative x-ray therapy and postoperative convalescence, blood from a blood bank, and an accurate control of fluid balance all permit extensive operative procedures in the head and neck region to be carried out with very commendable results, rapid convalescence, and minimum mortality and morbidity."

Scarcity of Men? Here's the Reason

When some women say there seems to be a scarcity of men, they know what they are talking about.

For the first time in American history, the 1950 census revealed, there are more women than men in our nation's population—1,430,000 more women, to be exact.

"According to present indications, the preponderance of women will continue to grow, with attendant increase in widowhood and dependency," it was stated editorially in a recent issue of the *Journal of the American Medical Association.*

The greatest difference occurs in the age groups over 45 years, where women outnumber men 1,000 to 956, it added.

Various factors contribute to the growing predominance of women over men. While the ratio of the two sexes at birth has been stable from year to year, about 1,055 men to 1,000 women, the ratio of deaths in men has been increasing. In 1930, this ratio was 1,210 deaths in men per 1,000 in women; in 1951, it was 1,333 men to 1,000 women.

The changing pattern of migration into and out of the United States also has been influential in the increase of the female population of the nation. In recent years, immigrants to this country have been predominantly women, and more men than women have been leaving the country. A net gain of 181,500 women over men occurred by migration during the five years immediately following World War II.

War deaths also have provided an additional factor for widening the margin between our male and female population.